**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Idebenone for treating Duchenne muscular dystrophy**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

| Section | Consultee/ Commentator | Comments [sic] | Action |
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| Wording | Duchenne UK | No comments. | - |
| Muscular Dystrophy UK | We do not propose alternative wording. However, it is essential that in any appraisal of the drug, NICE considers the costs of the treatment in relation to the unmet medical need and severity of the condition as well the costs of care and wider economic costs of Duchenne muscular dystrophy. | Thank you for your comment. No action needed. |
| Action Duchenne | The proposed remit seems to suggest that Puldysa (idebenone) be considered through the Single Technology (STA) process.  Although there are approximately 2,500 people living with Duchenne at any one time in the UK, only those not taking cortico-steroids would be eligible. We believe that due consideration has not been given to the size of the Duchenne population who would be eligible to receive Puldysa (idebenone).  At present, data supports a hypothesis that Puldysa (idebenone) only be available for those not taking concomitant glucocorticoids and is best applied when respiratory muscles weaken.  Consequently, there is a strong possibility that the number of those who would receive significant clinical benefits for those living with Duchenne is likely to be less than (around) a third of those living with Duchenne living in  the UK.  It is our belief that for these reasons Puldysa (idebenone) should come under the Highly Specialised Technology pathway | Thank you for your comments. Following the consultation exercise and scoping workshop, it was agreed that the appropriate route for this topic is as a Single Technology Appraisal (STA). |
| Santhera (UK) Limited | No comment | - |
| Timing Issues | Duchenne UK | Only one licensed treatment for DMD is available in the UK and this is only suitable for a subgroup of ambulant boys. DMD is a progressive life limiting condition and there is a significant and urgent need for suitable therapies for people living with DMD. | Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed. |
| Muscular Dystrophy UK | Respiratory decline in Duchenne muscular dystrophy leads to life-threatening complications. As there is currently no licensed medicine specifically aimed at slowing this decline, there is a significant urgency for this proposed appraisal. | Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.  No action needed. |
| Action Duchenne | Action Duchenne is committed to working to ensure that those living with Duchenne can benefit from treatments as quickly as possible. This is especially important given the severe and progressive nature of the condition.  The development of Puldysa (idebenone) could make a major difference for those living with Duchenne muscular dystrophy by helping improve respiratory management. At present there is no specific treatment  available through the NHS in England which aims to target underlying matters that reduce the respiratory functions of those living with Duchenne.  As Duchenne muscular dystrophy is a life limiting condition, we believe it is extremely important that the consultation is set out to avoid the complications and delays we saw in the assessment of Translarna (ataluren) - the  sole treatment available in England to treat the underlying cause of Duchenne. That process took over three years and caused many of those living with Duchenne and theirfamilies unnecessary stress. Time is of the  essence for those who have Duchenne.  It is important to note that our sense of urgency is increased, because Puldysa (idebenone) seeks to improve respiratory function management for those living with Duchenne, whether they are ambulatory or not. There are currently no specific treatments available for non-ambulatory patients and Puldysa (idebenone) could fill this void. | Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme.  No action needed. |
| Santhera (UK) Limited | No licensed medicine is currently available to treat patients with DMD who are experiencing respiratory function decline representing a population with a clearly defined unmet need. Respiratory failure results in significant morbidity requiring increasing levels of healthcare resource, an impact on quality of life and is still a leading cause of early death despite improving standards of care and supportive intervention.  Idebenone was granted Promising Innovative Medicine (PIM) designation by the Medicines and Healthcare Products Regulatory Agency (MHRA) in September 2016 and has been available via the Early Access to Medicines Scheme (EAMS) since 21st June 2017 for this population.  Given this, Santhera considers that there is clear urgency to provide early and consistent access to idebenone for patients in England | Thank you for your comments. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed. |
| Additional comments on the draft remit | Santhera (UK) Limited | Santhera have no additional comments on the draft remit. | Thank you for your comment. No action needed. |

Comment 2: the draft scope

| Section | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Background information | Duchenne UK | Project HERCULES is currently completing work on a natural history model of DMD that will provide more accurate estimates of time to different health states including loss of ambulation and uses respiratory and upper body function markers in the non ambulatory states. It also highlights the importance of the ability to weight bear. This work, undertaken by Professor Keith Abrams at the University of Leicester also suggests that whilst mortality rates have improved, 29 may not be an accurate reflection of average life expectancy.  Recent work published by Professor Muntoni et al (see https://doi.org/10.1371/journal.pone.0221097  suggests there are different trajectories which will be associated with reaching different health states at different ages – this is reflected in a broad age range at each stage that is not well reflected by the use of average ages. | Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. Where relevant, the natural history of DMD will be considered in any appraisal of idebenone. Scope unchanged. |
| Muscular Dystrophy UK | The background information is comprehensive but greater detail could be provided on the extent of respiratory weakness and the care required. For example, overnight ventilation necessitates 24 hour care, which increases the cost burden. Some patients will undergo a tracheostomy procedure. Respiratory infections frequently require systemic antibiotics and lead to hospitalisations.  It is also imperative that the impact of the condition on the patient’s family is fully captured. For example, through the cessation of employment to fulfil caring responsibility, or additional cost burdens such as specialist adaptations to the home. | Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. Where relevant, the nature of the condition and care required will be considered in any appraisal of idebenone. Scope unchanged. |
| Action Duchenne | We believe that the draft scope would benefit from making reference to the fact that in all the clinical trials of Puldysa (idebenone) it has proven to be safe and well tolerated. | Thank you for your comment. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. Scope unchanged. |
|  | Santhera (UK) Limited | NICE obtained the UK incidence of DMD (at 10.7 to 27.8 per 100,000 live born males) from the Mah et al., 2014 study. Further, NICE reported that there are 2,500 patients with DMD in the UK. This figure does not represent the target population in respiratory function decline intended for treatment with idebenone.  Taking this figure, as 80% of the UK population live in England, we can assume that 2,000 patients with DMD are residents in England. North star registry data reports that 24% of patients with DMD aged 14 and over are not taking glucocorticoids (Joseph et al., 2017). On that basis, the total number of patients with DMD eligible to receive treatment with idebenone will be fewer than 500 patients. Current clinical guidelines promote initiation and maintenance of steroid treatment from childhood for as long as is tolerated, a majority of patients will remain on this treatment into adolescence and in some cases into adulthood, it can therefore be expected that the proportion of patients not on glucocorticoids has been falling in recent years as adherence to guidelines improve. Therefore, the target patient group for idebenone as a proportion of the total DMD population is likely to further decrease in size.  The terms of the anticipated product licence for idebenone are very specific in terms of defining the eligible patient population (see under next section). Santhera considers that the current background information does not provide sufficient clarity of information about the natural history of respiratory decline phase in DMD and suggests including the following:  The progressive course of respiratory function decline in DMD is well documented and inevitable. Patients with DMD are at increased risk of respiratory complications due to their inability to clear airways and produce an effective cough. Progressive loss of respiratory muscle strength inevitably leads to reduced lung volumes, respiratory insufficiency and eventually failure (Bushby et al., 2010a,b).  Respiratory function decline occurs early from the age of 8 years old, and boys with DMD typically becoming abnormal at the time they become wheelchair bound. In the early stages of decline, whilst there is measurable decline in respiratory function, patients are usually non-ambulatory, unable to exert themselves, have reduced oxygen consumption and therefore often experience no dyspnoea symptoms. With continued weakening of respiratory muscles, symptomatic respiratory insufficiency is usually exhibited in individuals around the age of 15 years, corresponding to a 50% predicted loss of forced vital capacity (FVC), initially with episodes of nocturnal hypoventilation and sleep disordered breathing, altered daytime mood, tiredness, difficulty in staying awake and eventually cognitive impairment requiring night time ventilator support. As the disease progresses, incremental weakness in respiratory muscle strength and increased stiffness of the chest wall due to fibrosis results in a progressively worsening restrictive respiratory syndrome with daytime hypoventilation inevitably requiring full time ventilator support in all patients.  As respiratory function insufficiency worsens there is an increase in the risk of superimposed infections due to ineffective airways clearance, further compromised by episodes of bronchial mucus plugging, weakening and fatigue of inspiratory and expiratory muscles. Such episodes can result in repeated pneumonias, unplanned and prolonged hospitalisations, in more severe forms tracheal intubations, and ultimately, in emergency tracheostomy or early death within intensive care settings. This makes bronchopulmonary complications, such as airway infection, the single largest cause of unplanned hospital admissions in patients with DMD. In the UK, the proportion of unplanned hospital admissions of DMD patients attributed to respiratory crises has been estimated at 77.4% (Rodger et al., 2015). | Thank you for your comments. The background section of the scope aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. Scope unchanged. |
| The technology/ intervention | Duchenne UK | Yes. | Thank you for your comment. No action needed. |
| Muscular Dystrophy UK | Yes we believe that the description is accurate. | Thank you for your comment. No action needed. |
| Action Duchenne | We have nothing to add to this description. | Thank you for your comment. No action needed. |
| Santhera (UK) Limited | On 27th May 2019, Santhera submitted an application to the EMA for a Conditional Marketing Authorisation (MA) for idebenone. XXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX The conditional MA approval is anticipated in XXXXXXX  Idebenone received a PIM designation in DMD from the MHRA and has been available via the EAMS since June 2017. | Thank you for your comment. No action needed. |
| Population | Muscular Dystrophy UK | It should be made clear that Idebenone does not only apply to steroid-naive patients, but also to those who previously took steroids (and stopped taking them for various reasons). | Thank you for your comment. The population in the scope has been updated in light of the comment. |
| Action Duchenne | We believe that the scoping document could be more clear on the sub groups of people living with Duchenne that Puldysa (idebenone) is meant to be more effective for.  Since Puldysa (idebenone) will be used to treat respiratory dysfunction in those living with Duchenne, the population should reflect this. The Early Access to Medicines Scheme (EAMS) in the UK allows only those people in  respiratory decline to receive Puldysa (idebenone). It seems reasonable to use a similar criteria to define a point at which people are offered Puldysa.  This would reduce the number of people who would be eligible for treatment compared to the population defined in the Scope.  It should also be noted that the ongoing Sideros trial is testing the effectiveness of Puldysa (idebenone) in people who are taking concomitant corticosteroids. | Thank you for your comments. Idebenone will be appraised within its marketing authorisation. The population in the scope has been updated to specify people with respiratory dysfunction. |
| Santhera (UK) Limited | Santhera is seeking a conditional MA for the XXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX  Idebenone can be used in patients previously treated with glucocorticoids or in patients for whom glucocorticoid treatment is not desired, not tolerated or is contraindicated.  For idebenone, the target patient population is clinically distinct in that respiratory function decline is measurable using spirometry, and glucocorticoid use is known to clinicians caring for these patients. These patients are readily identifiable in the clinic and are amongst those with the highest unmet clinical need as there are no pharmacological treatment options available to slow the rate of respiratory function decline or prevent respiratory failure, one of the main causes of death in patients with DMD. There are no subgroups to examine within this population.  In line with the anticipated MA, Santhera requests that the population in the scope is amended as follows: *‘**people with Duchenne muscular dystrophy and respiratory dysfunction who are not using glucocorticoids.* | Thank you for your comments. Idebenone will be appraised within its marketing authorisation. The population in the scope has been updated to specify people with respiratory dysfunction. |
| Comparators | Duchenne UK | Details of current clinical practice in the NHS will vary depending on geography and health state. At present glucocorticoids are likely to be prescribed but different steroid regimes are in use.  The comparator should be standard of care, which will include ataluren for ambulant boys with a nonsense mutation, in appropriate sub-populations. | Thank you for your comments. Following the consultation and scoping workshop, it was concluded that established clinical management without idebenone is the appropriate comparator for the technology. No action needed. |
| Muscular Dystrophy UK | Yes the only comparator is standard respiratory care and management. There is no alternative treatment for patients with respiratory function decline who are not taking steroids. | Thank you for your comment. No action needed. |
| Action Duchenne | The other treatment used to manage the onset of respiratory problems for those who have Duchenne muscular dystrophy is corticosteroids.  Although corticosteroids are part of the Standards of Care for Duchenne, it is  important to note that some people living with the condition do not respond or cannot tolerate the side effects. In this group, Puldysa (idebenone) could provide an alternative to corticosteroids.  As such we believe that a comparator group based on Standards of Care could be complemented by a separate comparator group of people who are receiving neither Puldysa (idebenone) or corticosteroids. | Thank you for your comment. Idebenone will be appraised within its marketing authorisation. No action needed. |
| Santhera (UK) Limited | Santhera understands that there are no pharmacological treatments currently available to treat DMD patients with respiratory dysfunction who are not using glucocorticoids.  Non-pharmacological management includes volume recruitment/deep lung inflation techniques or manual and mechanically assisted cough techniques followed by non-invasive ventilation (Bushby 2010a).  Idebenone will not be considered as an alternative to either glucocorticoids (as idebenone treatment will be commenced after an independent decision to stop glucocorticoids) or ventilation (as idebenone will not be used as an alternative to any form of ventilation). Idebenone has the potential to slow down the rate of respiratory function decline and hence potentially to delay the time taken to the point at which ventilator support becomes necessary. | Thank you for your comment. No action needed. |
| Outcomes | Duchenne UK | Project HERCULES has worked with patients to identify disease states and outcomes that are important to patients and families. This work has bought together clinicians, patients, families and international clinical data sets. There are important outcomes not fully captured in DMD that are not fully captured in the scoping document:   * Ability to weight bear. The ability to weight bear allows for easier transfers (e.g. form wheelchair to bed or toilet). This has a huge impact on the amount of carer support that is required and the need for home and transport adaptations and the quality of life of the family unit. * Health Related Quality of Life. Project HERCULES has worked with ScHARR who reviewed current Quality of Life metrics against COSMIN criteria and identified the need for a Quality of Life metric that better captures the impact of DMD on patients and families. Following in depth interviews with patients and carers a number of themes emerged that it will be important to consider when looking at health related Quality of Life in DMD. * Carer Quality of Life There is a significant health related quality of life impact on families and carers which should be considered by NICE. Use, care and monitoring of ventilation equipment impacts on carers. | Thank you for your comments. The list of outcomes is not exhaustive, therefore information on those specific outcome measures can be submitted. The scope has been updated to include health related quality of life for both people with DMD and their families/carers. |
| Muscular Dystrophy UK | This technology is primarily concerned with preserving respiratory function. The majority of outcomes listed may not be relevant as this information was not collected in the DELOS phase 3 study. It is important that the outcome measures selected are focussed on the primary purpose of the treatment- to preserve respiratory function. | Thank you for your comments. Respiratory function is included in the outcome section. During the scoping workshop, it was noted that other outcomes such as cardiac function are also important measures for people with DMD therefore are included. Scope unchanged. |
| Action Duchenne | While the outcomes listed are wide ranging and are generally appropriate for this population, we believe that a set of outcomes with a closer alignment with the results observed in clinical trials of Puldysa (idebenone) should be considered – for example, the DELOS trial reported no treatment effect on upper limb strength or function, so the inclusion of “muscle strength”  as an outcome seems questionable.  We also believe there are other health related benefits that the scope could investigate. One of the long term outcomes which could be considered is the number of unplanned hospital admissions due to respiratory problems. A 2014 study on the burden of Duchenne muscular dystrophy highlighted the  costs to health services of admissions caused by a lack of proactive and preemptive care for Duchenne patients. It is possible an outcome of this nature could be developed to assess Puldysa (idebenone). | Thank you for your comments. The muscle strength outcome has been updated because data on muscle strength and motor function are collected in the company’s pivotal trial. The scope has also been updated to include change in hospital admission as an outcome. |
| Santhera (UK) Limited | The regulatory submission to the EMA for idebenone in DMD patients with respiratory dysfunction is based on the results observed in the phase III DELOS trial. As such the key relevant outcomes to assess the efficacy of idebenone in the population included in the anticipated MA are respiratory-related outcomes such as peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC), expressed as percentage predicted (PEF%p, FEV1%p and FVC%p).  The assessment of cardiac function, time to scoliosis and gastrointestinal functions are not relevant outcomes for the anticipated MA.  Clinically relevant morbidities, mortality, adverse effects of treatment and health-related quality of life are relevant outcomes.  Santhera requests that the outcomes in the scope are amended accordingly. | Thank you for your comments. We encourage companies to submit all relevant and available evidence for consideration. Scope unchanged. |
| Economic analysis | Duchenne UK | No comment. | - |
| Muscular Dystrophy UK | No comment | - |
| Action Duchenne | We have nothing to add | Thank you for your comment. No action needed. |
| Santhera (UK) Limited | In the STA process, NICE compares interventions by calculating the incremental cost-effectiveness ratio (ICER). In general, interventions with an ICER of less than £30,000 per QALY gained are considered to be cost-effective. This does not take into account wider societal benefits, and the rarity of disease which tends to result in higher drug acquisition costs.  Santhera considers that the cost-effectiveness threshold generally used by NICE within STAs would not be appropriate to assess idebenone in DMD given (i) the rarity of the disease and the consequent limited evidence base, both with and without idebenone treatment, and (ii) important benefits provided will not be captured by the quality adjusted life years measure of health benefit (e.g. benefit to carers, among others).  NICE reviewed ataluren in DMD under the HST programme, with a focus on the ambulatory phase of DMD. The committee recognised the high complexity of conducting a cost-effectiveness analysis in this disease area. A major reason was the lack of data available for this rare disease, leading to considerable uncertainty. The Evidence Review Group (ERG) noted the lack of evidence available on the long-term follow-up of patients with DMD. The committee acknowledged that the economic models developed by the manufacturer and the ERG had merits and flaws.  Given the fact that to date, the vast majority of clinical research in DMD has focussed on the ambulatory phase of the disease, there is even less evidence available for the non-ambulatory and respiratory decline phase of the illness, making it even more complex to assess a product designed for use in this phase.  Furthermore, idebenone is expected to be used exclusively in the context of a highly specialised service, in a limited number of highly specialised centres. Clinical care for the DMD patient population with highly complex clinical and social needs is concentrated in a small number of centres in England that deliver highly specialised and multi-disciplinary services to patients and their families. The standards of care are set by international guidance and supported by a UK clinical network (North Star). The introduction of any new technology in DMD must be managed carefully by expert clinicians who co-ordinate all aspects of patient care and adapt to the progressing disease condition in an individual patient. Patients with DMD who are in respiratory function decline are especially vulnerable to life-threatening deterioration of their condition or acute episodes of respiratory infection and they are highly reliant on the close monitoring and expert intervention of their clinical team. For patients with respiratory dysfunction this includes, in addition to neurological expertise, close involvement of specialist respiratory consultants and physiotherapists.  Santhera would like to work with NICE to ensure patients have timely access to idebenone. | Stakeholder comments on the suitability of this topic for the HST programme have been noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as a STA and will be scheduled into the work programme accordingly. |
| Equality and Diversity | Duchenne UK | No comment. | - |
| Muscular Dystrophy UK | No comment | - |
| Action Duchenne | We believe that everybody living with Duchenne should have access to approved treatments as quickly as possible.  The proposed remit could be considered discriminatory if access to an effective treatment is refused on grounds of cost for a life-limiting condition for which there is no cure.  It is important that the scope does not just consider costs, but also looks at the possibility and importance of extra time for families and people living with Duchenne, which Puldysa (idebenone) could potentially provide. | Thank you for your comments. When deciding whether or not recommend a technology where the evidence is available and relevant, the committee will take into account both the relative costs and health benefits associated with it (its cost-effectiveness). However, decisions are not based on the evidence alone, where appropriate, other factors, such as wider benefits not captured in QALY may be considered as well. Scope unchanged. |
| Santhera (UK) Limited | Given the nature of the disease, all DMD patients should be considered to have disability(ies). Hence, society has the obligation to look after this disadvantaged population and provide them with licensed treatments that can enable people with DMD to have a better quality of life for longer. | Thank you for your comment. If appropriate, the impact of any recommendation for idebenone on people with DMD who share protected characteristics will be considered by the committee. Scope unchanged. |
| Other considerations | Duchenne UK | No comment. | - |
| Action Duchenne | We have nothing to add | Thank you for your comment. No action needed. |
| Santhera (UK) Limited | No comment. | - |
| Innovation | Duchenne UK | Idebenone will be the first licensed treatment for DMD for most eligible patients given that ataluren is only available to ambulant boys with a nonsense mutation. Idebenone targets preservation of respiratory function in DMD which is aclear innovation in the treatment of DMD, as loss of respiratory function is a marker of disease progression, is associated with reduced quality of life ( in patients and carers) and respiratory failure is a leading cause of mortality in this disease.  As part of Project HERCULES, ScHARR carried out a review of current Quality of Life metrics using COSMIN criteria and found that there was a need to develop a disease specific measure to better capture quality of life in people living with DMD. In particular, the progressive nature of the condition meant the EQ5D and other commonly used tools did not have sufficient granularity to capture changed in health related quality of life within and between adjacent health states. A new DMD specific measure will be available from early 2020. In the absence of this metric, the Appraisal Committee should take steps to ensure all aspects of DMD that are important to patients and families are taken into consideration.  The Appraisal Committee should take in to account recent data and publications from Project HERCULES including the natural history data, burden of illness, and quality of life data which Duchenne UK can share with NICE during the appraisal process. | Thank you for your comments.The extent to which the technology may be innovative will be considered in any appraisal of the technology**.** We encourage companies to submit all relevant and available evidence for consideration. |
| Muscular Dystrophy UK | Yes, Idebenone is potentially the only treatment option for patients who are not taking steroids. It could delay the need for ventilation support and substantially improve quality of life of patients and carers. | Thank you for your comment. No action needed. |
| Action Duchenne | Yes we do.  Puldysa (idebenone) is non-mutation specific and non-ambulant specific. As such, it offers people living with Duchenne treatment options where none currently exist. Respiratory failure is the leading cause of death in Duchenne, and Idenbenone is able to preserve respiratory function in those not  taking corticosteroids.  It is also relevant to note that following a designation as a Promising Innovative Medicine (PIM) by the Medicine and Healthcare Products Regulatory Agency (MHRA), Puldysa (idebenone) is available via  the Early Access to Medicines Scheme (EAMS) in the UK.  The PIM shows it has the potential to lead to significant clinically beneficial outcomes for those living with Duchenne, which is a life-limiting and particularly debilitating condition.  As well as the impacts of preserving respiratory function for the patient  themselves, it is important to note the positive effects a drug that preserves respiratory function could have on the quality of life for care-givers, in particular parents and siblings. In Duchenne, where young men use power  wheelchairs and ventilators, this improvement is particularly important and should be included in the appraisal process.  We also draw attention to our point about unplanned hospital admissions above. | Thank you for your comments. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No action needed. |
| Santhera (UK) Limited | The introduction of idebenone will provide an innovative treatment to DMD patients with respiratory dysfunction who are not using glucocorticoids and for whom there is no available pharmacological treatment. Idebenone provides a ‘first of its kind’ treatment in this patient population as existing and future treatments being investigated for DMD are targeted at ambulatory patients, who do not yet suffer respiratory dysfunction, and are generally mutation-specific, further limiting the eligible population. Since idebenone is not restricted to specific genetic mutations, it addresses a serious unmet need in the DMD population.  Santhera has undertaken a substantial investment in clinical studies in order to further characterise the natural history of respiratory dysfunction in DMD which will help the medical community and patients to better understand and manage respiratory dysfunction in DMD. This was achieved by attempting to better understand the correlations between respiratory measures (PEF and FVC) and clinically relevant outcomes such as infections, hospitalisation due to respiratory complications, the need for assisted ventilation and death. Further work has been undertaken to understand the relationship between modifying the rate of respiratory function decline and delaying the time to needing assisted ventilation and the potential to reduce mortality rates. Several studies have now shown that treatment with idebenone can result in the sustained reduction in rate of respiratory function decline thereby demonstrating the clinical benefit provided by idebenone in an area of urgent and high unmet need. Idebenone has been recognised as an innovative medicinal product by the MHRA, which granted a PIM designation for idebenone in September 2016 and has been available via the EAMS since 21st June 2017.  People with DMD and respiratory dysfunction require significant support from carers in order to perform the functions of daily living. The introduction of idebenone for the treatment of DMD is likely to bring benefits to patients, carers and the wider society. Patients treated with idebenone are likely to have prolonged periods without the need for assisted ventilation. This can translate into a lower requirement for carer support and a higher degree of independence. Furthermore, data from the DELOS study showed that patients on idebenone had fewer respiratory tract infections, required fewer episodes of antibiotic use and fewer hospitalisations. | Thank you for your comment. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No action needed. |
| Questions for consultation | Duchenne UK | Duchenne UK has concerns about the use of the Single Technology Appraisal process to assess Idebenone. DMD is a rare paediatric progressive and life limiting condition. The evidence and cost effectiveness requirements of the STA process were not designed for these conditions and may not be well suited to assessing them.  We would ask that further consideration is given to inclusion in the HST programme which considered the only other authorised treatment for DMD, ataluren.  As with Ataluren, only a subgroup of patients will be eligible for Idebenone (in this case, those not taking glucocorticoids). | Stakeholder comments on the suitability of this topic for the HST programme have been noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as a STA and will be scheduled into the work programme accordingly. |
| Muscular Dystrophy UK | It is estimated that there are under 500 patients who would be eligible for Idebenone, and as a result of these patient numbers the drug would merit strong consideration for the HST appraisal route. The number of centres administering the drug is also likely to be limited to those which are part of the North Star Network. However, we believe that the HST programme is the most appropriate route for assessing this treatment. | Stakeholder comments on the suitability of this topic for the HST programme have been noted. Following extensive discussion, it was agreed that this topic is appropriate for consideration as a STA and will be scheduled into the work programme accordingly. |
| Action Duchenne | Please see comments above. | Thank you for your comment. |
| Santhera (UK) Limited | As described above, Santhera would like to work with NICE to ensure patients have timely access to idebenone.  It is expected that idebenone will be included in the existing NICE pathway ‘Muscles conditions’, under ‘Duchenne muscular dystrophy’, as an option for the treatment of respiratory dysfunction in DMD patients who are not using glucocorticoids, in line with its anticipated MA. (<https://pathways.nice.org.uk/pathways/neurological-conditions/neurological-conditions-overview#content=view-node:nodes-muscle-conditions>)  Santhera does not anticipate any barrier to adoption of idebenone specifically related to its use in clinical practice as none has been raised so far during the EAMS or during consultation with the clinical or patient communities. | Thank you for your comments. No action needed. |
| Additional comments on the draft scope | Duchenne UK | Duchenne UK are the leading UK research charity for Duchenne Muscular Dystrophy. We recognise the importance of HTA for new treatments and the challenges organisations like NICE face in making decisions about new treatments for rare diseases that may have an immature evidence base. We are leading an international multi stakeholder collaboration, Project HERCULES, to help address these challenges. We have brought together academics, clinicians, patients, HTA bodies including NICE and industry to develop key tools and evidence to support HTA in DMD. These include a natural history model based on probably the largest collection of DMD clinical data, a Quality of Life metric that captures things most important to patients and families, a UK burden of illness study and a core economic model. As such we are keen to share our work to inform the upcoming HTA for Idebenone for DMD. | Thank you for your comments. We encourage companies to submit all relevant and available evidence for consideration. |
| Santhera (UK) Limited | Santhera have no additional comments on the draft scope. | Thank you for your comment. No action needed. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

# Association of British Neurologists.