National Institute for Health and Care Excellence

Highly Specialised Technologies Evaluation

Eteplirsen for treating Duchenne muscular dystrophy

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

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Action Duchenne	Yes, the only concern is with IP and the license. Currently, a rival company has the patent on an exon skipping technology sequence (drisapersen) and therefore will the company be allowed to license its product here? I believe they are currently still in a legal dispute?	Comments noted. NICE will not publish guidance on the use of a technology that has not been granted a marketing authorisation in the UK. NICE aims to hold the first evaluation committee meeting as soon as possible after the technology gains a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency (NICE interim methods and process guide for Highly Specialised Technologies). No changes to the remit are required.
	Duchenne UK and Joining Jack	Yes	Comment noted. No changes to the scope required.

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	Genetic Alliance UK	We consider that the HST appraisal route (limited to three evaluations per year) should be reserved for novel products that do not match accepted paradigms of treatment. Since drisapersen was withdrawn from the UK, this will be the first medicine which treats the underlying cause of Duchenne muscular dystrophy in patients with these genotypes using exon skipping. This is an appropriate topic for HST evaluation.	Comment noted. No changes to the remit required.
	Muscular Dystrophy UK	Eteplirsen offers the prospect of slowing down the progression of Duchenne muscular dystrophy in the group of patients amenable to exon 51 skipping. There are no prescribed drug treatments which address an underlying genetic cause of Duchenne. The exception to this is Translarna, but this would only treat nonsense mutations causing Duchenne muscular dystrophy and not those patients amenable to the skipping of exon 51. Steroids – which are prescribed for a majority of children with Duchenne – are effective in prolonging ambulation but are often accompanied by severe side effects. Slowing the progression of Duchenne could decrease costs of care and the burden of the disease, thus improving the quality of life of those with the condition, as well as their family members and/or carers. It would be highly appropriate to refer this topic to NICE.	Comment noted. No changes to the remit required.

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Wording	Action Duchenne	I think there needs to be more consideration on the burden of Duchenne for young people and their carers there is growing evidence on the economic, social and education cost per year	Comments noted. The wording of the remit is intended to provide a brief summary of the evaluation committee's objective, and does not include specific outcomes for consideration other than benefits and costs. The outcomes being evaluated, and other considerations for highly specialised technologies, are summarised in the table in the scope. The committee's considerations will include the impact of the disease on carer's quality of life and whether the technology offers significant benefits other than health. See the NICE interim methods and process guide for Highly Specialised Technologies. No changes to the remit are required.
	Duchenne UK and Joining Jack	Yes	Comment noted. No changes to the remit required.
	Genetic Alliance UK	Yes, we understand that this is the standard wording	Comment noted. No changes to the remit required.

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	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	Comments noted. In its evaluation, the committee will take account of the nature of the condition, impact of the new technology, cost to the NHS and Personal Social Services, value for money, impact of the technology beyond direct health benefits and the impact of the technology on the delivery of the specialised service (see the NICE interim methods and process guide for Highly Specialised Technologies). NICE encourages all consultees to submit this evidence in their submissions to NICE, which will then be considered by the evaluation committee. No changes to the remit required.
Timing Issues	Action Duchenne	It is urgent, the company developing drisapersen treatment withdrew their application to EMA so there is no potential for exon skipping therapy and families have been waiting at least 7 years in the UK. Some young people with Duchenne were treated and felt they had benefited from treatment, but have significantly deteriorated because of the delays and timeframe involved	Comments noted. No changes required.

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	Genetic Alliance UK	Currently there are no treatments available on the NHS in England for Duchenne muscular dystrophy patients with a deletion in exon 51 which treat the underlying cause of the disease. Even with the recent positive decision on ataluren, there is only a very small overlap in the populations which would respond to the two medicines. This is because where patients have a nonsense mutation in the region of exon 51, in most cases this would require skipping of more than one exon, and so eteplirsen would not be effective (see Yokota et al (2012) Exon skipping for nonsense mutations in Duchenne muscular dystrophy: too many mutations, too few patients?, Expert Opinion on Biological Therapy, 12:9, 1141-1152,). For patients with a (non-nonsense) mutation correctable by exon 51 skipping, eteplirsen is the only treatment able to address this signficiant unmet medical need, which causes progressive muscle weakness and premature death. Even in the case of patients who respond to this medicine, disease progression appears to be largely irreversible. Patient access is therefore an urgent issue.	Comments noted. No changes required.
	Muscular Dystrophy UK	Duchenne muscular dystrophy is an exceptionally severe condition with a high unmet medical need. Progression and loss of function is rapid. A licence from the EMA may initially approve the drug for use only in ambulant boys, meaning a swift appraisal would be necessary in order to try and ensure no eligible patient loses ambulation before NICE guidance is issued and the drug available in clinic.	Comments noted. No changes required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Action Duchenne	The average lifespan is now 29 years old with Duchenne and creatinine supplementation is not approved, there is insufficient evidence. What is included in the standard of care guidelines is vitamin D supplementation, which helps support bone health	Thank you for your comments. The background section has been updated.
	Duchenne UK and Joining Jack	There is an error on page 2 where drisapersen has been mentioned instead of eteplirsen.	Comment noted. The background section has been updated.
	Genetic Alliance UK	We note that the background information has been copied directly from the recent HST scoping of drisapersen, and suggest the mention of drisapersen in the second to last paragraph be corrected to eteplirsen.	Comment noted. The background section has been updated.
	Muscular Dystrophy UK	The background information is broadly accurate, although we believe additional information is needed in order to capture the severity of the condition particularly around respiratory weakness and ventilation. For example, overnight ventilation necessitates 24 hour care, which increases the cost burden. Some patients will undergo a tracheostomy procedure. Respiratory and cardiac weakness place patients at risk of hospitalisation and of sudden death. Patients also undergo scoliosis surgery (the insertion of iron rods into the back) which is risky and can require a lengthy stay in hospital. It is also important to capture some of the impact of the condition on the patient's family. For example, through the cessation of employment to fulfil caring responsibility, or additional cost burdens such as specialist adaptations to the home.	Comments noted. The background section is intended to provide a brief summary of the disease and how it is managed. It is not designed to be exhaustive, therefore no changes to the scope are needed. Consultees are encouraged to expand on the condition and its treatment in their evidence submissions. No changes to the scope are required.

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	Sarepta Therapeutics	We recommend the following changes to the background: **1)** It is caused by the presence of different types of mutations on the X-chromosome in the gene for dystrophin, **the missing** protein that is important for maintaining normal muscle structure and **function which is missing in patients diagnosed with Duchenne.** 2) The incidence of Duchenne muscular dystrophy is approximately 1 in **3500**–6000 male live births 3) Eteplirsen is the therapy (not drisapersen, which is written in the document)	Comments noted. The background section has been updated.
The technology/ intervention	Action Duchenne	Yes, there could be more information about the chemistry here that it is unique and different to that of drisapersen and other potential exon-skipping compounds	Comment noted. This section is intended to provide a brief summary of the technology and therefore no changes to the scope are needed.
	Duchenne UK and Joining Jack	yes	Comment noted. No changes to the scope are needed.
	Muscular Dystrophy UK	Yes, we believe the description is accurate.	Comment noted. No changes to the scope are needed.
Population	Action Duchenne	There is no mention of the 6-minute walk test, this was the primary endpoint. The change in 6-minute walk test is clearly a clinically meaningful endpoint and also there is variation according to function at baseline for those who have a low measure means there decline will be steep and those on the other end gradual. A clear median baseline measure has been used for most recent clinical trials. Genetic modifiers also play a great role here some young people respond better to steroids and also have a later loss of ambulation other genotypes within the dystrophin gene have a different disease trajectory. Exon 51 skippable young people tend to have a normal natural history.	Comments noted. This section defines the population covered by the technology's marketing authorisation. Please refer to the comments on the outcomes section of the scope. No changes to the scope are needed.

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	Duchenne UK and Joining Jack	yes	Comment noted. No changes to the scope are needed.
	Muscular Dystrophy UK	Yes, we believe the population is currently defined appropriately. An EMA licence may define the population further.	Comment noted. No changes to the scope are needed.
Comparators	Action Duchenne	Yes standards of care guideline treatment such as steroids the best regimen and dosage is currently being established for Duchenne	Comment noted. No changes to the scope required.
	Duchenne UK and Joining Jack	yes	Comment noted. No changes to the scope required.
	Muscular Dystrophy UK	Yes, and they include regular specialist physiotherapy, self-management exercise techniques, steroid treatment and in later stages of the condition ventilation support is needed, such as cough assist machines, other non-invasive forms of ventilation, or a tracheostomy procedure. Those that relate to ambulation, such as physiotherapy and steroid treatment, would be likely to continue to be administered with eteplirsen.	Comment noted. No changes to the scope required.
Outcomes	Action Duchenne	As above, there needs to be a clear mention of the 6-minute walk test as a clinically meaningful endpoint. The time to wheelchair cannot not be measured as this depends on many factors and mortality is not appropriate or applicable in this case. There is no mention of the North Star score which has been used in recent trials and the managed access agreement for translarna. There is no mention of patient reported outcome measures, these are very important.	Comments noted. Mortality is a standard outcome which is assessed in all highly specialised technology evaluations. Mortality data is necessary for the economic model; it is used to calculate quality-adjusted life years associated with the intervention and comparators. The 6-minute walk test and North Star Ambulatory Assessment have been added as examples for assessing walking ability. Time to wheelchair has been redefined

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			as time to loss of ambulation; the scoping workshop attendees agreed that this was a meaningful and measurable outcome. Workshop attendees agreed that loss of ambulation is defined as inability to walk a few steps independently. Patient reported outcome measures are captured within 'health-related quality of life'. Outcomes are broad to allow flexibility in the evaluation; outcomes can be defined on the basis of available evidence. NICE encourages all consultees to submit evidence for important outcomes in their submissions to NICE, which will then be considered by the evaluation committee.

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	Duchenne UK and Joining Jack	The impact of the disease on the immediate and wider family needs to be further assessed. The potential health and social benefits to the whole family of a new, approved treatment should be carefully considered.	Comments noted. In its evaluation, the committee will take account of the nature of the condition, impact of the new technology, cost to the NHS and Personal Social Services, value for money, impact of the technology beyond direct health benefits and the impact of the technology on the delivery of the specialised service. This will include the impact on and benefit to carers (see the NICE interim methods and process guide for Highly Specialised Technologies). Consultees are encouraged to submit evidence for important outcomes. No changes to the scope are required.
	Genetic Alliance UK	The outcomes listed are appropriate, however we also add time to assistive ventilation.	Thank you for your comments. Time to assistive ventilation is captured within the outcomes listed in the scope. It has been added as an example of how to measure lung function.

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	Muscular Dystrophy UK	Maintaining cardiac and respiratory function are critical aspects of the management of Duchenne muscular dystrophy. However, given the ambulant patient group for whom the EMA would be likely to licence the drug, it is important that any technology appraisal is mindful of the fact that benefits for cardiac and respiratory function could only be properly studied on a longer term basis. Therefore, ambulation and associated outcomes should be the primary focus.	Comment noted. Consultees are encouraged to submit evidence for important outcomes. No changes to the scope required.

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	Sarepta Therapeutics	The outcome measures to be considered include: • **6MWT** • **Loss of Ambulation** • **Ability to Rise Indecently (%)** • **NSAA** • **Western Blot** • **IHC (% PDPF)** • **IHC (BIOQUANT Intensity)** • **RT-PCR (Exon Skipping)** • **Pulmonary Function (FVCL, FVC % p, MIP %p, MEP% p** • adverse effects of treatment • health-related quality of life (for patients and carers). • **Number of falls**	Comments noted. These outcomes suggested are all captured within the outcomes in the draft scope. Outcomes are broad to allow flexibility in the evaluation; outcomes can be defined on the basis of available evidence. The final scope includes examples for some outcomes. Based on discussion at the scoping workshop, time to wheelchair has been redefined as time to loss of ambulation; the scoping workshop attendees agreed that this was a meaningful and measurable outcome. Workshop attendees agreed that loss of ambulation is defined as inability to walk a few steps independently. NICE encourages all consultees to submit evidence in their submissions to NICE, which will then be considered by the evaluation committee.

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Equality and Diversity	Action Duchenne	This is a very important issue because there will be those amenable to exon 51 skipping who participated in drisapersen trials and have received treatment, there needs to some flexibility to allow those who wish to receive eteplirsen. It is also not fair on those families who were in the open-label AVI Biopharma trial in the UK in 2009 and when the trial was discontinued. Families have been receiving the drug for 3-years in the US.	Comment noted. Issues relating to clinical trial enrolment cannot be addressed in a NICE evaluation of a highly specialised technology. The technology will be evaluated within the boundaries of its marketing authorisation and the committee's recommendations are based on the clinical and cost-effectiveness evidence presented. Any potential equality issues will be considered during the course of the evaluation and the committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population. No action required.
Innovation	Action Duchenne	Exon skipping technology is innovative and widely believed to help slow the progression of Duchenne. What is unique about this compound is the chemistry. Most new generation sequences are using the PMO backbone as it is widely believed the most promising moving forward.	Comments noted. All consultees are encouraged to describe the innovative nature of eteplirsen in their submissions to NICE, which will then be considered by the evaluation committee. No changes to the scope required.

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	Duchenne UK and Joining Jack	Wider health, social and financial impact on families	Comments noted. All consultees are encouraged to describe the innovative nature of eteplirsen in their submissions to NICE, which will then be considered by the evaluation committee. No changes to the scope required.
	Genetic Alliance UK	Since the marketing authorisation application for drisapersen was withdrawn in the EU, we understand that this will be the first medicine of its kind (an antisense oligonucleotide) licensed in the EU, and represents a stepchange in the management of the condition, as the first medicine which treats the underlying cause of the disease in this subpopulation of DMD patients	Comments noted. All consultees are encouraged to describe the innovative nature of eteplirsen in their submissions to NICE, which will then be considered by the evaluation committee. No changes to the scope required.
	Muscular Dystrophy UK	Yes, the technology is one of the first to target an underlying genetic cause of the condition and exon skipping is an innovative technology. Clinical trials indicate that the drug slow the progression of the condition to a clinically significant degree.	Comments noted. All consultees are encouraged to describe the innovative nature of eteplirsen in their submissions to NICE, which will then be considered by the evaluation committee. No changes to the scope required.
Other considerations	Action Duchenne	It is good to consider here that the compound has been relatively safe, no serious or moderate adverse events reported over long-term treatment	Comment noted. No changes to the scope required.

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Questions for consultation	Muscular Dystrophy UK	Most boys with Duchenne are not diagnosed until they start displaying symptoms, unless there is a family history of the condition. The first signs of Duchenne are usually problems with motor skills and muscle function, for example difficulty running and jumping, getting up off the floor, enlarged calf muscles and/or delayed speech development. If a blood test is done, high levels of a protein called creatine kinase (CK) are seen. CK is normally found in muscle but when muscles are damaged it leaks into the bloodstream. Duchenne has to be confirmed by genetic testing usually on a blood sample. Further genetic testing or a muscle biopsy may also be performed in some cases.	Comments noted. No changes to the scope required.