NICE National Institute for Health and Care Excellence

NICE guidance

Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

Highly specialised technologies guidance
Published: 22 February 2023

www.nice.org.uk/guidance/hst22

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces HST3.

1 Recommendations

1.1 Ataluren is recommended, within its marketing authorisation, as an option for treating Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in people 2 years and over who can walk. This is only if the company provides ataluren according to the commercial arrangement.

Why the committee made these recommendations

This evaluation reviews existing trial data, additional evidence collected as part of the managed access agreement for NICE highly specialised technologies guidance 3, and new real-world evidence (evidence collected outside clinical trials) on ataluren.

Duchenne muscular dystrophy, with a nonsense mutation in the dystrophic gene, is a rare and progressive condition. Over time it causes muscle weakness resulting in the loss of the ability to walk and reductions in respiratory ability, and it significantly reduces life expectancy. Current treatment options are limited.

Real-world evidence studies were used to estimate the treatment benefits of ataluren compared with best supportive care. The company did not use data from the managed access agreement in its economic model because it believed it did not provide the most appropriate outcome measures. The evidence provided, along with feedback from clinicians and people with the condition, suggests that ataluren is likely to slow down disease progression and delay the loss of the ability to walk. Evidence for improvements in later stages of the disease and improved survival with ataluren is limited and highly uncertain but ataluren may also improve outcomes once the ability to walk has been lost.

The cost-effectiveness estimates are uncertain because of how treatment benefits were estimated. There is uncertainty around the estimated costs of ataluren in the company's model. The way that carers' quality of life was included in the model was not realistic so this was considered qualitatively. That is, it was discussed in depth during decision making based on patient and clinical expert input on the factors that are important to carers. The cost-effectiveness estimates are uncertain because of the limitations in the clinical effectiveness data. But, with the commercial arrangement agreed after the second

committee meeting, the cost-effectiveness estimates for ataluren are below the range that NICE usually considers acceptable for highly specialised technologies. So ataluren is recommended.

2 Information about ataluren

Marketing authorisation indication

2.1 Ataluren (Translarna, PTC Therapeutics) has a conditional marketing authorisation for 'the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The price for ataluren is £2,532 per box of thirty 125-mg sachets, £5,064 per box of thirty 250-mg sachets and £20,256 per box of thirty 1,000-mg sachets (excluding VAT; BNF online accessed September 2022).

2.4 The company has a commercial arrangement. This makes ataluren available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by PTC Therapeutics, the views of people with the condition, those who represent them, clinical experts, NHS England and a review by the external assessment group (EAG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene

3.1 Duchenne muscular dystrophy (DMD) is a severe, progressive, X-linked recessive disorder that mainly affects males. DMD with a nonsense mutation is caused by a single base variation in a person's DNA, which leads to incomplete dystrophin production in the skeletal, smooth and cardiac muscle fibres. Dystrophin production is usually affected from birth and symptoms of DMD often appear by the time the child is 3 years old. The main symptom of DMD is motor dysfunction but, as the disease progresses, the gastrointestinal tract and vital organs such as the heart are affected. People with DMD have a decline in physical functioning, with subsequent respiratory and cardiac failure that leads to death, usually before they are 30.

Impact of the condition on people with DMD and their families

3.2 The committee considered the submissions from patient organisations and patient experts. The patient experts explained that DMD significantly affected people with the condition and their carers. Their submissions outlined that the condition limits the types of activities people with DMD can do, and puts strains on maintaining friendships. The patient experts highlighted the psychological

impact of losing the ability to walk, and of the onset of respiratory symptoms. They said that ataluren provided hope to people with DMD and their carers because it slowed down disease progression and allowed carers more time to adjust to the different stages of the disease. They explained that people with DMD need assistance with everyday tasks, such as getting dressed and getting out of bed. They also described how caregiving becomes more challenging once someone stops being able to walk and the disease progresses. The patient experts said that delaying the loss of the ability to walk is very important to people with DMD and carers. Once this happens, maintaining upper limb function is valued highly because this means the person with DMD can still do some activities and tasks. And this reduces the impact on the carer to an extent. The committee concluded that DMD has a substantial impact on both people with the condition and carers.

Clinical management

Managed access agreement

3.3 Ataluren has been available as part of a managed access agreement since the original NICE highly specialised technologies guidance for ataluren was published in 2016. The managed access agreement required data collection from people having treatment and their families. Before this, the only treatment option was best supportive care. Best supportive care for DMD includes treatment with corticosteroids, which is associated with a delay in the loss of walking but can have significant adverse effects. The clinical expert said that ataluren would not reduce the need for corticosteroids and that they would be given in addition. Other interventions include cardiac and respiratory monitoring and ventilation support, occasional inpatient orthopaedic intervention, spinal surgery and rehabilitation. Dietary advice (and, in some cases, gastric feeding), prevention and treatment of bone fragility, management of the complications of long-term corticosteroid therapy, and psychosocial support may also be needed. Clinical care is provided by a range of healthcare professionals, depending on local services, including neurologists or paediatric neurologists and neuromuscular specialists, rehabilitation specialists, neurogeneticists, paediatricians and primary care physicians.

Clinical effectiveness

Data sources

3.4 The main evidence sources used by the company for this review came from 2 real-world studies: The STRIDE study, which included people who had DMD caused by a nonsense mutation in the dystrophic gene, were aged 2 and over, and had received ataluren. This study was carried out mainly in Europe. The CINRG study was designed to capture the natural history of the disease in people with DMD who had best supportive care, and was mainly carried out in North America. In the original highly specialised technologies guidance, 2 randomised controlled trials comparing ataluren with placebo over 48 weeks formed the main evidence base (Study 007 and Study 020). The primary outcome measure in these trials was the 6-minute walk distance (6MWD). The clinical expert said that the 6MWD is not routinely collected in clinical practice in England. The patient experts said 6MWD matters less to them than other outcomes, for example stamina in undertaking certain tasks. The company explained that it preferred to use the real-world evidence studies because it collected data on loss of the ability to walk and on other relevant disease timepoints, which it believed was a more relevant set of outcome measures than the 6MWD. It also noted that the real-world evidence sources provided longer-term data than the clinical trials. The committee was aware that ataluren has been available as a treatment option as part of a managed access agreement and that at the time of the original guidance it had been expected that this data would inform the present review. The managed access agreement collected data from people having treatment and their carers. The company explained that it did not use data from the managed access agreement in its economic model because the primary outcome measure used was the North Star Ambulatory Assessment (NSAA). It outlined that the scores using this outcome measure generally improve in people with DMD up to 7 years of age because of usual child development, which made it difficult to show a significant treatment effect for ataluren for patients in the NHS. It also noted that the age at first symptom had not been collected. This is an important prognostic factor and its absence made matching with sources of natural history data difficult. The committee agreed to consider the data from STRIDE and CINRG for this review but also took into account the findings of the managed access agreement.

Indirect treatment comparison

3.5 The company used propensity score matching to indirectly compare the clinical effectiveness of ataluren with best supportive care because STRIDE and CINRG did not include a comparison of ataluren against best supportive care. In the company's base case, this involved matching patients in STRIDE to those in CINRG based on prognostic factors. The company used 4 prognostic factors in its matching (age at first symptoms, age at first corticosteroid use, duration of deflazacort, and other steroid use). The EAG said that it considered the company's matching methodology to be appropriate but noted some limitations. For example, there were some imbalances between the groups, which, along with methodological limitations, may have affected the results. It was also not clear if the different locations of the 2 studies might affect the results (see section 3.4). The EAG considered that these limitations added to the uncertainty of this comparison. The company's indirect comparison showed that ataluren delayed the median time to the loss of the ability to walk by a median of 5.4 years compared with best supportive care (17.9 years compared with 12.5 years, $p<0.0001$). This comparison also estimated a delay in reaching a forced vital capacity (FVC) of less than 50%, but this result was not statistically significant. The company said that the STRIDE data was not mature enough to estimate outcomes, at later disease time points, of respiratory function or survival (see section 3.4). The company also provided 2 more indirect comparisons for ataluren compared with best supportive care. This included one that matched people in the managed access agreement data to those in the NorthStar registry (a natural history study of people with DMD having best supportive care in the UK). The company said this comparison was limited by the use of the NSAA outcome measure and because of difficulties in matching (see section 3.4). The company believed that this was why this indirect treatment comparison failed to show meaningful differences in outcomes. The company also provided an indirect comparison between Study 019 (a long-term follow-up study of people having ataluren) and CINRG, which the company provided to supplement its base case analysis. The EAG noted that the company's additional indirect comparisons provided less compelling evidence than the STRIDE and CINRG comparison, and said it had similar concerns over limitations in these 2 additional analyses. The committee acknowledged that ataluren is likely to slow down the progression of the disease, based on the results from the company's indirect treatment comparison. The committee concluded that the STRIDE and CINRG indirect

comparison was the most appropriate to use in decision making, but that its results were uncertain.

The company's economic model

Model based on ambulation status and FVC

3.6 In the previous evaluation of ataluren, the company developed a semi-Markov model. It had 6 health states, representing the progression of DMD from the ambulatory phase (when the person can walk) to the non-ambulatory phases and death. In this previous model, transitions between health states used the results of the 6MWD from 2 randomised controlled trials of ataluren compared with placebo (Study 007 and Study 020). For the current review, the company presented a new economic model, which used partitioned survival models (see section 3.7) in each health state (ambulatory, non-ambulatory; FVC above 50%, below 50% and below 30%). The company explained that the health states in the new model corresponded to those defined in project HERCULES (a DMD natural history model) and better reflected the disease course than the model used in the original guidance. The company also said the model aligned well with outcomes included in the STRIDE and CINRG studies, which allowed use of longer-term data and avoided reliance on the 6MWD outcome (see section 3.4). The EAG noted that its clinical experts had said that in general the model structure was appropriate but that the model did not account for scoliosis, which had a substantial impact on quality of life. The committee agreed that the company's model structure was appropriate for decision making, but that data informing the model was limited, particularly at later disease stages. The committee highlighted that the model included only 1 ambulatory health state, which did not cover the full range of functioning and quality of life across the ambulatory stage of the condition. The committee considered that a model including additional ambulatory health states may have better captured disease progression in a more appropriate way (see section 3.10). It was aware that assumptions about quality of life in the ambulatory health state had a significant impact on the cost-effectiveness results (see section 3.9). It also noted that scoliosis was not accounted for in the model structure.

Survival modelling

3.7 The company fitted standard parametric models to both STRIDE and CINRG data at each model timepoint (see section 3.6). The company in its original base case used log-logistic models to estimate the age at which people lose the ability to walk, and the age at which predicted FVC was less than 50%. It also applied a log-normal model to CINRG data to estimate the age at which predicted FVC was less than 30% for best supportive care. And it assumed a relative benefit for ataluren because there was no data available for this outcome in STRIDE (the amount of benefit is considered academic in confidence by the company and cannot be shown here). The EAG assumed the same model selection for each health state as that in the company's original base case. But it noted that the models selected did not appear to provide a good fit to the data for several of the modelled health states. The EAG also noted that the company had not considered more flexible models, which may have provided a better fit to the data. The company updated its base case after technical engagement to adopt a Weibull model for all health states, based on an EAG sensitivity analysis. The company considered that the cost-effectiveness analysis was relatively insensitive to the choice of standard parametric model, and so did not do analyses with a broader range of models. The committee considered that this was true for the company and EAG base case analyses but may not be the case if other assumptions in these analyses were changed. The EAG also highlighted that its clinical experts considered that the modelled health benefits (delays to loss of the ability to walk and in reaching respiratory milestones) estimated from the company's model appeared to be optimistic (the model also included additional benefits assumed to occur from starting treatment early; see section 3.8). In response to the evaluation consultation document (ECD), the company adopted the committee's preferred modelling choices, as used in the EAG base case. In addition, the company provided additional survival modelling analysis using more flexible models. The company noted however that these models had limitations because they suggested counterintuitive differences in survival between the health states, with some worse health states having better survival. This was not appropriate because it did not follow the progressive nature of Duchenne and so was not clinically valid. The committee considered that the company's original base case model choices, as used in the company's and EAG's base case analysis, were the most appropriate to use for decision making. But it noted that the results were uncertain because of the poor fit of the models to the

data.

Assumed additional early treatment benefits

3.8 The company assumed additional relative treatment benefits of ataluren compared with best supportive care because of the licence extension to allow use in people aged 2 years and over (previously this had been 5 years and over). The company based these assumptions on clinical expert input from a Delphi panel. It included the assumed additional benefits in the model by artificially shifting the ataluren survival curves to the right by an additional number of years. This increased the amount of time spent in each health state (the number of additional years assumed in each health state is considered to be academic in confidence by the company and cannot be reported here). The company said that this was because earlier treatment would be associated with better outcomes compared with that estimated from the STRIDE and CINRG indirect comparison. The EAG noted that very few people had received ataluren in STRIDE before they were 5 years old and that there was no other direct evidence to show that starting treatment early provided additional benefit. The committee was aware that the company's economic model assumed everyone would have treatment with ataluren at 2 years old. They considered that this was inconsistent with published evidence and clinical expert opinion that most diagnoses of DMD in England are at around 4 years, and that there is currently no national screening programme for DMD. In its response to the ECD, the company presented additional information that showed that the condition can be diagnosed before 4 years. It added that the rate of early diagnoses has increased. The patient organisations also highlighted that they have seen diagnosis earlier than 4 years. The committee pointed out that the figure of 4 years was a mean age of diagnosis, which meant that some children would be diagnosed before 4 years, but others would be diagnosed later. The committee concluded that it would not include the additional assumed treatment benefits related to early treatment of ataluren in its preferred analysis.

Utility values

Treatment-dependent utilities

3.9 Health state utility values in the company and EAG base case analysis were assumed to depend on which treatment people were having. These values were taken from a DMD Delphi panel study (Landfeldt et al. 2020), which involved 6 Swedish neuromuscular experts who completed the Health Utility Index 3 (HUI3) questionnaire. Using this source resulted in utility values that were substantially higher for ataluren compared with best supportive care in each health state:

- ambulatory health state: ataluren 0.93, best supportive care 0.62
- non-ambulatory health states: ataluren 0.32, best supportive care 0.16.

The company said that it used treatment-dependent utility values because they were supported by clinical experts and patient organisation submissions. It also explained that its economic model did not capture additional disease symptoms and benefits of ataluren. The committee noted that the Landfeldt et al. study was designed to ask experts to complete the HUI3 questionnaire for the ambulatory state based on 2 different descriptions of mobility (the 6MWD and assuming a mean age of 13), which reflected the trial results from Study 007 and Study 020 at 48 weeks. So the committee considered that the study did not reflect any utility benefits from ataluren in addition to those related to ambulation, but could simply reflect slowing of disease progression with ataluren. Study 007 and Study 020 showed a numerical increase in quality of life for people having ataluren compared with best supportive care at 48 weeks. But these results were not statistically significant and again could not differentiate between improvements that were because of changes in ambulation and those that were independent of ambulation. The company said that this was likely because of the short duration of those trials and explained that changes in quality of life would take longer to show. The EAG noted that the company applied treatment-dependent utilities from the beginning of the model time horizon and applied them throughout the model, even when treatment with ataluren had stopped. The EAG said its clinical experts had difficulty when commenting on the appropriateness of treatment-dependent utilities

because of the limited evidence informing this. The EAG's clinical experts said that significant quality of life differences between treatments was unlikely in the ambulatory health state. One EAG expert said that ataluren may improve quality of life in non-ambulant health states because of a reduced risk of scoliosis. The clinical and patient experts said, in their response to technical engagement, that they believed it was appropriate to use treatment-dependent utilities because of the benefits of treatment with ataluren. The committee was aware that the company had not provided empirical evidence of quality of life differences from people having ataluren or best supportive care treatments. The committee was also aware that the utilities assumed for the ambulatory health state had the largest influence on the cost-effectiveness results for ataluren. The clinical expert at the committee meeting said that ataluren could reduce the risk of developing scoliosis and delay respiratory symptoms in non-ambulatory health states because it would allow muscle strength to be preserved for longer during puberty. The committee was aware that, in the original guidance, the analysis did not include different utility values for ataluren compared with best supportive care within the same health state but did consider the impact of scoliosis on quality of life. The committee concluded that the company's economic model for this review did not include the impact of scoliosis and so it was plausible that the health state utility may be higher in non-ambulatory health states for people having ataluren compared with best supportive care. The committee also concluded that the company's treatment-dependent utility values were not appropriate for the ambulatory health state.

3.10 In its response to the ECD, the company provided additional evidence, including clinical trial outcomes, which it believed supported applying treatment-dependent utilities in all model health states. The EAG commented that, even with this additional evidence, there was still no empirical preference-based evidence to support treatment-dependent utilities. Patient representatives, in their response to the ECD, further highlighted the benefits of ataluren, particularly in the ambulatory health state. They said that ataluren improved important aspects of the condition, including stamina, quality of walking and psychological benefits. They also said that ataluren use was likely to result in fewer falls and fractures. The clinical experts agreed with this but noted that data on falls is not routinely captured in clinical practice. The committee considered these stakeholder responses but noted that all the benefits highlighted related to ambulation and

that the company's model may not capture the additional potential benefits of ataluren. The committee considered that a better model structure, with more than 1 ambulatory health state, could have been developed by the company to address this issue. This could have allowed a better estimate of ataluren's quality of life benefits over the ambulatory period of the condition. But the committee was also aware that the data needed to inform additional health states may be limited. It considered that the company had not provided robust evidence to support its use of treatment-dependent utility values in the ambulatory health state. But it agreed that people treated with ataluren may experience health-related quality of life benefits in the ambulatory health state that were not captured fully in the company's model (see section 3.6). But the size of any such health utility gains would likely be substantially lower than that estimated by the company's modelling. The committee considered that the effect of this on cost effectiveness was unclear. The committee also agreed that treatment-dependent utilities were plausible in the non-ambulatory health states, because of a reduced risk of scoliosis.

Carer quality of life

3.11 The company assumed 2 carers in its analysis and used absolute values for carers' quality-adjusted life years (QALYs) from the Landfeldt et al. 2017 study. The company's approach estimated substantial incremental carer QALY gains for ataluren. The EAG highlighted that the approach taken by the company implicitly assumed that for carers, once the person they were caring for died, either the QALYs gained by carers were equal to zero, or these QALYs are not valued by society. The EAG therefore believed that this approach was inappropriate and in its base case used a carer disutility approach (which applied a disutility value to each health state). It said this was in line with methods used in previous highly specialised technologies evaluations in which carers' quality of life was included in the analysis. This included the previous evaluation of ataluren. The company noted that the EAG's analysis resulted in a small reduction in QALYs for ataluren compared with best supportive care. This was because ataluren extended the time spent in each health state, which increased patient QALY values but also increased carer disutility over the lifetime of the company's model. The company believed that this was counterintuitive, because ataluren was estimated to provide a survival gain compared with best supportive care. This resulted in

fewer QALYs estimated for ataluren compared with best supportive care for carers. The company updated its approach during technical engagement to apply carer QALYs until the median overall survival timepoint across both treatment groups in the model. It explained that this was an attempt to compensate for the potential overestimate of carer benefit in its original base case. The EAG considered that the company's updated approach was still inappropriate because it still did not value QALYs of carers once the person they were caring for had died. The committee acknowledged the testimonies of the patient experts, who outlined the benefits of ataluren treatment on carers (see section 3.2) and agreed that including carer quality of life in the economic model was challenging. The committee considered that the company's approach was not appropriate because it assumed that carer QALYs should equal zero in the economic model when the patient died. It also noted that there were apparent differences between the outcomes of the EAG approach and the testimonies of the patient experts in relation to QALY loss for carers. It therefore concluded that it would exclude estimated carer QALYs from its preferred analysis and instead would consider the impact on carers in its decision making in a qualitative way. In response to the ECD, the company updated its base case to remove carers' QALYs from its model, but highlighted the substantial impact of the condition on carers. Responses from patient representatives further highlighted the benefits of ataluren for carers and expressed concern that carer quality of life was not included in the model. The committee acknowledged these concerns and explained that the method the company had used to include carer QALYs was inappropriate. The disutility approach adopted by the EAG resulted in a negative cumulative QALY gain for carers, which made ataluren less cost effective. Because of this the committee preferred to consider carer quality of life qualitatively. It emphasised that carer quality of life was considered in depth during its decision making, including the responses from stakeholders, which the committee used to assess the potential impact of ataluren on carers. The committee highlighted that it included the impact of ataluren on carers when considering the most plausible cost-effectiveness results.

Stopping treatment

Rate of treatment discontinuation in the model

3.12 The company assumed that people would stop taking ataluren treatment at a constant rate based on data from STRIDE (the rate used is considered academic in confidence by the company and cannot be reported here). This rate was applied until the modelled formal treatment stopping rule (see section 3.13). The EAG said the observed treatment discontinuation rate may have double counted the events that would be captured in the company's proposed stopping rule. It said that its clinical experts said that the rate used in the company's base case appeared implausibly high given the severity of the condition and lack of alternative treatment options. The EAG provided an analysis that reduced the discontinuation rate by 50% to explore the impact of this on cost effectiveness. It explained that changes to time on treatment only affected costs in the company's economic model and did not affect the estimated health outcomes. The committee considered that the company's estimated discontinuation rate likely overestimated treatment discontinuation and so underestimated ataluren treatment costs. In response to the ECD, the company provided an updated treatment discontinuation rate estimated from STRIDE, which accounted for discontinuation because of loss of ambulation. The EAG agreed that the company's updated estimate was the most appropriate to use in the economic model. The committee concluded that the company's updated treatment discontinuation rate was the most appropriate to use in its decision making.

Treatment stopping rule

3.13 In the managed access agreement, ataluren treatment was stopped no later than 6 months after the person with DMD was no longer able to walk. The committee was aware that wording had been removed from the summary of product characteristics for ataluren that said that there was no evidence ataluren had any efficacy once someone had lost the ability to walk. The company, in its base case, proposed extending the treatment stopping rule used in the managed access agreement to the point at which predicted FVC was less than 50%. It noted that this was the timepoint at which night-time ventilation was likely to be

needed. But the company and clinical experts highlighted that any stopping rule based on predicted FVC would be challenging because it was difficult to accurately measure the height (which is needed to assess FVC) of people with DMD who cannot walk. The EAG explained that STRIDE, which the company used to estimate ataluren's effectiveness (see section 3.4), did not impose a consistent stopping rule. So it was unclear how the treatment benefits estimated from STRIDE aligned with any stopping rule assumed in the company's economic model. The clinical expert said that clinicians would want to continue using ataluren after their patients lost the ability to walk because of the benefits in upper limb and respiratory function. The clinical and patient experts said that the decision to stop treatment should be taken after discussion between patients, carers and clinicians. The NHS England commissioning expert agreed with these experts' views. The committee noted that the company's economic model did not provide a scenario analysis for if there was no formal clinical stopping rule. It was also aware that changing the stopping rule scenarios in the company's economic model only affected total costs and did not change the estimated benefits. The committee agreed that it would not include a formal stopping rule in its preferred analysis, and that the decision to stop treatment would be taken after discussion between patients, carers, and clinicians (see section 3.17). Based on clinical advice, the committee preferred to use the time when predicted FVC reached less than 30% as a way to estimate treatment costs in the economic modelling. But it acknowledged that this may not align with how treatment is stopped in clinical practice. The committee considered that there may be other reasons for stopping treatment (such as non-respiratory reasons and non-adherence to treatment). In response to the ECD, the company updated its base case to align with the committee's preferred assumptions on the stopping rule in the model to estimate treatment costs.

Cost-effectiveness estimates

Committee-preferred assumptions

3.14 The company's updated base case analysis resulted in an incremental cost-effectiveness ratio (ICER) below £100,000 per QALY gained (the exact ICER is considered confidential by the company and cannot be reported here). The

committee recalled that this analysis did not account for all its preferred assumptions, which were:

- Assuming treatment-independent utility values for the ambulatory health state and treatment-dependent utility values for non-ambulatory health states (see section 3.9).
- Removing carer QALYs from the cost-effectiveness analysis and considering carer impacts qualitatively (see section 3.11 and section 3.16).
- Removing early treatment effect benefits (see section 3.8).
- A lower treatment discontinuation rate for ataluren based on the company's updated estimated rate (see section 3.12).
- Not imposing a defined treatment stopping rule; but for the cost-effectiveness analysis, costs in the model would be those if treatment is stopped when predicted FVC is less than 30% (see section 3.13).

Using these preferred assumptions, and the new commercial arrangement submitted for the second committee meeting, the ICER estimate was below £100,000 per QALY gained (the exact ICER is considered confidential by the company and cannot be reported here). Ataluren did not meet the criteria for a QALY weighting (see section 3.15). The committee noted the high levels of uncertainty in the evidence base for ataluren and in the economic modelling but recalled its commitment to consider the effect of treatment on carer quality of life, independent of the economic model.

QALY weighting

3.15 The committee understood that NICE's interim process and methods of the highly specialised technologies programme (2017) specify that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is usually considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is shown by the

number of additional QALYs gained and by applying a 'QALY weight'. The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 QALYs. It discussed the number of undiscounted QALYs in the analysis. It noted that the company's updated base case in response to the ECD resulted in more than 10 undiscounted QALYs. The committee recalled that it considered that the company's treatment-dependent utility values were only appropriate for non-ambulatory states (see section 3.9). Using this assumption resulted in the estimated number of undiscounted QALYs being much lower than 10. The committee concluded that ataluren did not meet the criteria for applying a QALY weighting.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

Indirect benefits

3.16 The patient experts said that ataluren allowed people with DMD to have a more fulfilling life. They said it meant that education could be continued and friendships maintained. Patient expert submissions said that ataluren treatment might allow the parents of people with DMD to stay in employment for longer because it slows down disease progression and provides hope to carers and people with DMD. The committee had agreed to take a qualitative approach to considering the impact of ataluren treatment on carers. It also considered that it might be appropriate to view the benefits differently depending on the time in a child's life when they are gained, compared with best supportive care (that is, delaying loss of the ability to walk in childhood and adolescence). It noted that no empirical evidence was provided for this. The committee concluded that ataluren is likely to have a positive impact on people's lives beyond its direct health benefits.

Other factors

Equality issues

3.17 Some stakeholders said it was important that people with DMD did not have to travel excessive distances for treatment. The committee acknowledged that clinical expertise would usually be concentrated at a small number of centres. One stakeholder also said that the current managed access agreement stopping rules did not allow use in people who could not walk, and that this may discriminate against older people with DMD. The committee noted that it had not included a formal treatment stopping rule in its preferred assumptions and so this was not an issue. No other potential equality issues were identified by the committee.

Innovation

3.18 The clinical and patient experts said that ataluren is the first treatment licensed to treat DMD caused by a nonsense mutation in the dystrophin gene. They explained that ataluren's mechanism of action resulted in a step change in managing DMD caused by such mutations in the dystrophin gene. The committee concluded that ataluren was innovative.

Conclusion

Recommendation

3.19 The committee took into account its preferred assumptions (see section 3.14), indirect treatment benefits (see section 3.16), and other factors. It considered that the most plausible ICER was below £100,000 per QALY gained (the exact ICER is considered confidential by the company and cannot be reported here). The committee concluded that ataluren was cost effective compared with best supportive care. So it recommended ataluren for routine use in the NHS for treating DMD resulting from a nonsense mutation in the dystrophin gene, in

people 2 years and over who can walk.

4 Implementation

4.1 Section 8 (6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if someone has Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene and the doctor responsible for their care thinks that ataluren is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Peter Jackson
Chair, highly specialised technologies evaluation committee

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Alan Moore
Technical lead

Christian Griffiths
Technical adviser

Celia Mayers

Project manager

ISBN: 978-1-4731-5034-8