NICE National Institute for Health and Care Excellence

NICE guidance

Vamorolone for treating Duchenne muscular dystrophy in people 4 years and over

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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

1 Recommendation

1.1 Vamorolone is recommended, within its marketing authorisation, as an option for treating Duchenne muscular dystrophy (DMD) in people 4 years and over. Vamorolone is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

Current treatment options for DMD are limited. Corticosteroids such as prednisone are used to slow progression of the condition.

Evidence from a clinical trial shows that vamorolone improves muscle function compared with placebo. But, it is uncertain whether vamorolone is similar at improving muscle function outcomes, and how well it works in the long term, compared with currently available corticosteroids. Compared with prednisone, the evidence suggests that vamorolone is likely to have fewer side effects, although to what extent is uncertain.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates for vamorolone are within the range that NICE considers an acceptable use of NHS resources. So, it is recommended.

2 Information about vamorolone

Marketing authorisation indication

2.1 Vamorolone (Agamree, Santhera) is indicated for 'the treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older'.

Dosage in the marketing authorisation

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

Price

2.3 The anticipated list price of vamorolone is £4,585.87 per 100 ml of a 40 mg/ml oral suspension (excluding VAT; company submission).

2.4 The company has a commercial arrangement. This makes vamorolone available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Santhera, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Duchenne muscular dystrophy (DMD) is a rare and severe genetic condition that causes muscle weakness and progressive disability from childhood to adulthood. DMD is caused by a mutation in the gene that codes for dystrophin, a protein important for muscle cells. Because the dystrophin gene is found on the X-chromosome, the condition mainly affects boys and men. DMD symptoms usually start in children aged 3 to 5 years, but sometimes symptoms can occur in children as young as 2 years. Early symptoms include large calf muscles, delays in sitting and standing, Gower's movement and an unusual gait when walking. Children with DMD begin to experience a decline in muscle strength in their hips and legs. This leads to a loss of abilities such as running, climbing stairs and, eventually, walking. Muscle weakness then spreads to the arms and neck, causing loss of arm and hand function over time. As children get older their muscles progressively get weaker. This means that, when they reach adulthood, they will likely need help with all self-care activities such as eating, drinking, toileting, dressing, washing and moving. When children lose the ability to walk independently and need mobility aids such as wheelchairs, they need healthcare appointments to monitor their spine, heart and sleep-disordered breathing. The spine can develop scoliosis, which may need surgery. Also, the heart may develop cardiomyopathy, which may need treatment with angiotensin-converting enzyme inhibitors and beta-blockers. In the later stages of the condition, overnight non-invasive ventilation and cough assistance is needed to help clear the airways. The life expectancy of people with DMD depends how quickly and intensely muscle weakness progresses. But it has been reported to be an average of less than 30 years. Because symptoms start in children as young as 2 years, people with DMD live their whole life with gradually decreasing physical

mobility. This decrease in mobility means a higher dependence on other people, including families and carers, to support them in their daily lives.

Impact of the condition

3.2 The committee considered submissions from patient organisations and patient experts. The patient experts explained how DMD significantly affects people with the condition, as well as their families and carers. Their submissions outlined how devastating the diagnosis can be. They explained the substantial physical, logistical, emotional, psychological and financial burden for people with DMD and their families and carers. The patient experts explained how the condition limits the types of activities people with DMD can do, and detailed the psychological effect of losing the ability to walk. They explained that people with DMD need assistance with everyday tasks, such as getting dressed and getting out of bed. They also described how caring becomes more challenging once the condition progresses and the person with DMD becomes unable to walk. The patient experts said that delaying the loss of the ability to walk is very important to people with DMD, and their families and carers. Once the ability to walk has been lost, maintaining upper limb function is valued highly because this means people with DMD can still do some activities and tasks. The patient experts explained that even small levels of functioning, such as the independent use of a straw or finger function, can be important. They explained how significant growth and self-image can be to people with DMD. Often, the point at which people with DMD lose the ability to walk is when their peers at school become more independent, which can cause feelings of isolation. The committee concluded that DMD has a substantial effect on people with the condition, as well as their families and carers.

Clinical management

Treatment options

3.3 Currently, treatment options for DMD include corticosteroids, specifically prednisone, prednisolone or deflazacort. The aim of corticosteroids is to reduce

the symptoms of DMD. They have shown significant benefits in:

- slowing the progressive loss of muscular strength
- extending the length of time the person is able to walk independently
- avoiding the need for scoliosis surgery
- preserving upper limb function for longer
- delaying the start of cardiac and respiratory function decline.

But corticosteroids can also affect people's quality of life because of their side effects, which include osteoporosis, reduced bone strength and increased risk of spinal fractures. People may also have vitamin D and gastroprotective treatments to prevent adverse reactions to corticosteroids. The patient experts detailed that the most important side effects to manage were weight gain, negative behaviour changes, growth restriction, reduced bone density and delayed puberty. The clinical experts explained the need to manage the short-term effects of treatment while attempting to minimise the long-term progression of muscle weakness and other complications. The clinical experts explained that there are likely some people who switch corticosteroid treatment to better manage side effects. For example, they explained how a person might move to using deflazacort to manage weight gain. They explained that there is also a possibility of switching between daily use and intermittent use of corticosteroids to manage the level and severity of side effects. The patient experts said they would welcome treatment options with less severe side effects. At the second committee meeting, the committee discussed a survey submitted by patient groups that focused on the impact of adverse events from treatment with corticosteroids. The survey included responses from people with DMD, and family members and carers of people with DMD (see section 3.17). The committee concluded there is a need for effective treatments for DMD with less severe side effects than standard corticosteroids.

Vamorolone positioning

3.4 Vamorolone is anticipated to be used as an alternative to currently available

corticosteroids. The company explained that vamorolone differs from traditional corticosteroids because of its structure, which alters its activity. The clinical experts explained that people with DMD should have treatment as early as possible, and they would expect to use vamorolone for children who had not had treatment for DMD. The clinical and patient experts also noted that there would likely be some people having current treatments who would want to switch to vamorolone for its anticipated better safety profile. In its response to draft guidance consultation the company noted that in VISION-DMD (see section 3.5), switching from 0.75 mg/kg of prednisone to 6 mg/kg of vamorolone after 24 weeks retained the benefit in motor function endpoints. Also, in ongoing trial VBP15-006 they found that no one who switched from long-term corticosteroids to vamorolone 6 mg/kg developed any symptoms suggesting adrenal insufficiency. The committee asked why the company did not include treatment sequencing options in its economic model. The company noted that this was because existing guidelines for treating DMD do not distinguish between which corticosteroid to start treatment with. At draft guidance consultation, stakeholders advised that there may be some people who are unable to continue treatment with corticosteroids (see section 3.22), and the option to include treatment sequencing would have been helpful. The committee concluded that, for most people, vamorolone would likely be started for those who have not had previous treatment with corticosteroids. But it acknowledged that there are some people who would have vamorolone after existing corticosteroids, for example because of side effects.

Clinical effectiveness

VISION-DMD trial

3.5 The clinical-effectiveness evidence for vamorolone was mainly taken from VISION-DMD, a 24-week phase 2b, double-blind, randomised, placebo- and active-controlled trial followed by a 20-week treatment extension period. The study was done at 33 centres, 6 of which were in the UK. The trial included 121 people aged 4 to 6 years with DMD who had not had treatment for the condition. They were randomised equally to 4 treatment arms: vamorolone 6 mg/kg/day, vamorolone 2 mg/kg/day, prednisone 0.75 mg/kg/day or placebo. The

primary outcome in the trial was time to stand. Other muscle-function outcomes included the 6-minute walk test, time to climb, time to run or walk 10 m, knee extension, elbow flexor muscle strength and the North Star Ambulatory Assessment score. VISION-DMD also investigated safety and health-related quality-of-life outcomes through the condition-specific DMD-QoL utility measure. The committee heard how the mean age in VISION-DMD was 5.42 years for vamorolone 6 mg/kg/day and 5.54 years for prednisone. The committee noted the comment from clinical experts that the earlier treatment is started the better and that, if treatment is started in people over 6 years, the benefit is likely to be reduced. The clinical experts explained that the mean age of starting treatment is affected by the average age of diagnosis being age over 4 years. The committee was also aware of the issue that VISION-DMD was done in a treatment-naive population. This is because most of the current DMD population are already having corticosteroids in England. The committee concluded that the VISION-DMD population is appropriate for people who have not had treatment for DMD. It also noted that most of the clinical evidence is in people who have not had treatment with corticosteroids before.

Muscle-function outcomes

3.6 After 24 weeks, there was a clinically meaningful improvement with vamorolone and prednisone compared with placebo for all muscle-function outcomes included in VISION-DMD. Improvements across all muscle outcomes were similar but slightly less with vamorolone than prednisone. But the company said that these numerical differences were not statistically significant. It concluded that the 2 treatments could be considered equivalent. The EAG did not think that vamorolone could be considered equivalent to prednisone. It did not think that the overlapping of confidence intervals was because of similar treatment effects. Rather, it thought that it may have been because of the small size of the trial and the anticipated variability in treatment outcomes. The EAG explained that the numerical differences in muscle-function outcomes could be clinically meaningful for people with DMD, and their families and carers. It thought that, because of the poorer muscle-function outcomes, vamorolone would likely not be as effective as prednisone in slowing down disease progression over the long term. The committee understood that a lack of statistical significance from overlapping confidence intervals does not necessarily mean equivalence in outcomes. It

highlighted that a non-inferiority trial would be needed to come to this conclusion. The committee acknowledged that this would need a much larger sample size and would be challenging in a rare disease like DMD. The company explained that VISION-DMD was powered to compare vamorolone with placebo, and not to detect differences between vamorolone and prednisone. The clinical experts said that the consistency in overlapping outcomes should be taken into consideration. The committee highlighted that vamorolone was numerically worse than prednisone (but not statistically significantly so) across all muscle-function outcomes compared with prednisone. It thought that this should also be considered. The patient experts explained that, even if muscle outcomes were marginally lower, many people would choose vamorolone for potentially better safety outcomes. In response to draft guidance consultation, the company and EAG explored modelling scenarios around muscle-function outcomes (see section 3.10). The clinical experts at the second committee meeting noted that vamorolone did not show worse muscle-function outcomes than corticosteroids, either in clinical practice or in the trials. The committee concluded that vamorolone improved muscle-function outcomes compared with placebo. But it had not been presented with any robust evidence to suggest that vamorolone was equivalent to prednisone.

Adverse events

3.7 VISION-DMD also investigated the side effects of vamorolone and prednisone for people with DMD. The committee heard that the number of adverse events was similar between vamorolone and prednisone, and there were no meaningful differences after 24 weeks. When considering only moderate to severe adverse events, there were no incidences of weight gain, behavioural, immune-related issues, gastrointestinal, or skin or hair change adverse events with vamorolone over 24 weeks. But, with prednisone, there were low rates of weight gain, gastrointestinal, and skin or hair change adverse events, and moderate rates of immune-related and behavioural issues. The EAG questioned the definition of 'moderate to severe adverse events', given that an adverse event of special interest was already defined as any event that was 'severe and sudden in onset'. The committee understood that the main potential benefits of vamorolone may be a reduced incidence of specific side effects such as stunted growth, behavioural issues and poor bone health. It asked whether the assumptions on

reduction in side effects, based on the limited data, were reasonable and could be expected to continue over the long term. The clinical experts highlighted that bone health outcomes are an important measure because fractures can lead to the early loss of walking. They highlighted that, while VISION-DMD showed that vamorolone had marginally better bone health outcomes, it is difficult to capture bone fracture events in a short-term clinical trial. The EAG noted that the follow up in VISION-DMD was short and the data from it uncertain. But it explained that the data suggested the risk of important adverse events is lower with vamorolone than with prednisone, and that this is a potentially important benefit. The EAG also noted that excluding less severe events resulted in a substantially lower incidence of side effects for both vamorolone and prednisone compared with the overall trial data. The patient experts explained that side effects are very important to people with DMD, and their families and carers. They highlighted that behavioural issues can have a big impact, and noted that these issues can often affect decisions around stopping treatment. The patient experts also mentioned the importance of appearance to people with DMD. The committee noted there were slightly more instances of Cushingoid symptoms with vamorolone than with prednisone, and that this would affect appearance. The company explained that this small rate of Cushingoid symptoms was 1 event in the trial, so should be interpreted with caution. The patient experts also signalled how important growth outcomes are to people with DMD. The committee acknowledged the importance of reducing side effects for people with DMD, and their families and carers. It also understood the data limitations associated with a small, short-term trial, but that this was not uncommon in a rare disease area such as DMD. The committee concluded that vamorolone is likely to reduce the incidence of important moderate to severe adverse events compared with prednisone, but that the extent of this benefit was uncertain because of the limited trial evidence.

Economic model

Company's modelling approach

3.8 The company's economic model was based on the HERCULES natural history model of disease progression for people with DMD. HERCULES is a UK-led project

started by Duchenne UK to develop tools and evidence to support health technology assessment for new DMD treatments. The model comprised 8 progression-based health states and death. The health states were defined and structured around a person's ability to walk, hand-to-mouth function and need for nighttime or fulltime ventilation. The model had a starting age of 4 years, consistent with people newly diagnosed with DMD who have not had treatment. The committee recalled that most of the clinical evidence is in people who have not had treatment with corticosteroids before. The company incorporated evidence from VISION-DMD, the natural history model and a range of literature sources to populate its economic model. The model included transition probabilities and extrapolations for vamorolone, prednisone, deflazacort and no treatment. The company assumed that all these corticosteroids were equivalent. The no-treatment transition probabilities were informed by the placebo arm of VISION-DMD. People moved from the active-treatment transition probabilities to no-treatment transition probabilities on stopping treatment. The EAG thought that this did not capture the treatment pathway in DMD because some people may have more than 1 corticosteroid treatment over a lifetime (see sections 3.3 and 3.4). The company compared vamorolone with a standard-care arm comprising a mix of prednisone and deflazacort use. The EAG considered the structure of the model to be appropriate in addressing the decision problem. It did not think that the company's approach to modelling a comparison against a blended standard-care arm was appropriate. The EAG thought that this ignored differences in prednisone and deflazacort efficacy and safety. The committee concluded that the overall model structure was appropriate for decision making, but that treatments should be compared against each other in a fully incremental analysis. In its response to draft guidance, the company provided a fully incremental deterministic analysis.

Natural history model

3.9 The committee noted that the Project HERCULES natural history data was likely the best available source of information. But it questioned whether the extrapolations and progression through health states were appropriate. The EAG explained that the underlying data in the HERCULES model was not representative of the UK population. The committee noted how there was a kink in the natural history model overall survival curve at 30 years, when around 70%

of people were alive. The committee noted that the median survival expected for people with DMD from the literature is around 30 years. But the natural history model predicted a greater life expectancy than this. The clinical experts explained that survival has shifted from about 20 years to 30 years over recent years because of improvements in standard care. But they added that it is hard to predict future life expectancy in this disease area. The clinical experts acknowledged that the natural history model may have overestimated survival compared with current clinical practice. For example, they do not expect 10% of people to be alive at 50 years, as was predicted in the company's modelled time horizon. The clinical experts explained that all milestones were probably overestimated in the model. They thought that this was potentially optimistic because it attempted to predict improvements in standard care. The committee noted that the model may have overestimated life expectancy for DMD. In its response to consultation, the company updated its mortality data in the model. It changed the model to apply a per-cycle mortality risk. The company also applied a minimum mortality risk based on the highest risk from natural history data, the natural history model, or data from Broomfield et al. (2021), which was a study of life expectancy in people with DMD. The EAG believed that the company's approach was the most plausible method available. The committee concluded that the company's updated method was sufficient for decision making, although it was still associated with some uncertainty.

Long-term muscle-function outcomes

3.10 The clinical evidence for vamorolone used to inform the model mainly came from the 24-week VISION-DMD follow up (see section 3.5). The company considered that vamorolone and prednisone were equivalent when considering muscle-function outcomes. It also assumed that deflazacort was equivalent to prednisone. This meant that all the treatments would result in the same transitions, informed by the HERCULES natural history model. The committee recalled its conclusion that there was no robust evidence that vamorolone was equivalent to prednisone (or deflazacort). It also recalled that it was plausible that vamorolone might result in slightly worse muscle-function outcomes and overall disease progression (see section 3.6). So, the committee considered that modelling based on an assumption of equivalence was not reliable. The committee noted that any difference in muscle-function outcomes between

treatments would affect costs and health benefits. It recalled the EAG's view that the small numerical differences between treatments seen in VISION-DMD could be meaningful to people with DMD, and their families and carers. It would also affect cost-effectiveness outcomes when extrapolated over 50 years. The committee said it would consider the company's assumption of equivalent treatment effect. But it wanted to see a scenario that assumed a difference in muscle-function outcomes between treatments based on VISION-DMD. In response to draft guidance, the company provided responses from a Delphi panel. This concluded that the numerical differences in muscle outcomes seen in VISION-DMD were not clinically relevant. The company also suggested that the numerical differences in VISION-DMD were because of the small size of the study instead of any meaningful difference in efficacy. But it provided scenarios in which vamorolone had 5% and 10% lower efficacy than the other corticosteroids. The EAG provided an analysis that compared the results of prednisone and vamorolone against placebo for muscle-function outcomes. The analysis suggested vamorolone had a 32% lower efficacy in muscle-function outcomes compared with prednisone. But the EAG acknowledged that this was a crude estimate, so included a 20% reduced efficacy for vamorolone in its base case, which was the midpoint between its estimate and the company's. At the second committee meeting, the clinical experts disagreed with modelling a difference in muscle-function outcomes and highlighted data from long-term extension studies and the NorthStar database, which indicated that people who switched from prednisone to vamorolone had no drop in muscle-function trajectory. The committee agreed that neither the EAG's base case nor the company's scenarios for reduction in muscle-function outcomes were based on robust methodology. It concluded that there was considerable uncertainty in both approaches. As there was no robust evidence to base its decision on, it preferred to consider modelling that did not include a difference in muscle-function outcomes between vamorolone and the comparators, but took into account the important uncertainty in this approach.

Modelling adverse events

3.11 The company included 24-week moderate and severe adverse events from VISION-DMD in its economic model. In addition, the model also included stunted growth, incidence of fracture (spinal and other), and scoliosis. Adverse events of

special interest included weight gain, behavioural issues and Cushingoid features. Acute events were diarrhoea, vomiting, fever and cough. Data for adverse events of special interest and acute events for vamorolone and prednisone was extracted from VISION-DMD. The placebo arm of VISION-DMD was used to represent the incidence of events for people not having treatment. Incidence of stunted growth for prednisone and deflazacort was based on a 6-year follow up of a case series of children and young adults aged 10 to 15 having daily corticosteroids (72%) but was assumed to be 0% for vamorolone. Incidence of behavioural issues was based on the prednisone arm of VISION-DMD for prednisone and deflazacort (5%) but was assumed to be 0% for vamorolone. The EAG noted that the company only included moderate to severe events in its analysis. It added that excluding less severe events resulted in substantially lower incidences being reported in the model compared with the overall trial data. The EAG noted that it is vamorolone's side-effect profile that has been suggested to provide the most value to people with DMD. This meant that it was important to investigate the impact of all adverse events. The clinical experts explained that the rates of side effects are not necessarily constant over time. They explained that most side effects generally increase with time as exposure to corticosteroids increases, but that behavioural issues can improve as people get used to treatment. The EAG highlighted that most of the quality-adjusted life year (QALY) gains in the model for vamorolone came from a reduction in adverse events when compared with standard care. The EAG also noted that behavioural issues made up almost all carer QALY gains for vamorolone in the model (see section 3.16). The committee agreed that it was important for assumptions around adverse events and, in particular, behavioural issues to be valid. It accepted that side effects comprised the main source of health benefits for vamorolone, so needed to be modelled properly. The committee recalled that a reduction in adverse events would be highly valued by people with DMD, and their families and carers. At the first committee meeting, the committee was not convinced that the modelling of adverse events was sufficiently robust and requested alternative analyses. It said it would want to see further justification from the company on how adverse events had been modelled. The committee said it also wanted clarification from the company that adverse events had not been overestimated for the comparator treatments in the model. Finally, it said it would like to see further sensitivity analyses done, including a scenario that used all of the adverse-event data from VISION-DMD. In its response to draft guidance, the company updated its base case to include all adverse events of special interest

from VISION-DMD. The company also updated its assumptions on the length of several adverse events including behavioural issues (see section 3.17) after receiving opinions from clinical experts. The EAG noted that the company's updated model addressed some of the committee's concerns around adverse-event modelling, but some issues remained. This included an arbitrary assumption that mild adverse events were 25% of the disutility for moderate to severe adverse events. The committee acknowledged that it had been presented with new evidence and analysis from the company in response to its requests at the first committee meeting, and explored the new evidence in its discussions.

Stopping treatment

Treatment-discontinuation assumptions

3.12 The company used 24-week treatment-discontinuation data from VISION-DMD to inform the time on treatment for vamorolone. Prednisone and deflazacort time-on-treatment data was taken from the Cooperative International Neuromuscular Research Group (CINRG), which provided a much longer follow up. People who stopped treatment with vamorolone, prednisone or deflazacort in each cycle then had no-treatment transition probabilities. This increased the speed of progression through the model, which reduced both costs and QALY outcomes. The committee heard how the CINRG discontinuation data was reported for about 14 years compared with 24 weeks in VISION-DMD. This data was extrapolated over the 50-year time horizon in the cost-effectiveness model. The EAG considered that extrapolating less than a year of data surrounding stopping treatment to a lifetime was highly uncertain. It also thought that the company's extrapolation of stopping vamorolone lacked face validity. The company's model predicted that people having vamorolone would stop treatment much quicker than those having prednisone or deflazacort. The committee considered this lacked validity. It thought that a better safety profile with vamorolone should increase tolerability and reduce the number of people stopping treatment. The EAG's base case assumed that people having vamorolone would stop treatment at the same rate as deflazacort. This was because deflazacort had the longest time on treatment of the 2 standard-care treatments. The EAG argued that this could potentially be considered conservative because the safety profile of vamorolone is expected to be better than deflazacort. The company said that the

EAG's approach of using deflazacort as a proxy led to an overestimation for time on treatment with vamorolone. The company thought that, because the prednisone data was the most mature, it might have been more appropriate to use that than data for deflazacort. The committee noted that the treatment-discontinuation curve for deflazacort seemed to plateau over the long term. The company also suggested using alternative data from the NorthStar registry, which is a UK DMD dataset. The committee acknowledged that other sources of data could provide relevant evidence. The clinical experts explained that very few people would stop corticosteroid treatment completely. They explained that it is more likely that doses are reduced or changed to more intermittent treatment. The clinical experts also raised concerns that the prednisone and deflazacort extrapolations were markedly different. They would expect treatment duration to be more similar between the 2 corticosteroids in use in clinical practice. The committee thought that the company's extrapolation was likely to have substantially underestimated time on treatment with vamorolone. It also thought that it did not align with the proposed benefits of vamorolone. The committee concluded at the first committee meeting that the company's modelling of vamorolone treatment discontinuation being faster than other corticosteroids was not suitable for decision making. It thought that the EAG's assumptions were preferable, but still highly uncertain. It also concluded that further modelling of treatment discontinuation was needed. In its response to draft guidance, the company aligned its base case on treatment discontinuation for vamorolone with the committee's preferred assumption of assuming that vamorolone has equal treatment discontinuation to deflazacort.

Proposed stopping rule at nighttime ventilation

3.13 At the first committee meeting the company noted the possibility of a treatment stopping rule for vamorolone. But it provided limited further details on the clinical reason for this, the criteria on which it could be based, or on its appropriateness in practice. In the company's response to draft guidance, it proposed a stopping rule for vamorolone once nighttime ventilation was started. The company noted that no one in any of the clinical trials for vamorolone had had nighttime ventilation, so there was no evidence that the benefits of using vamorolone when nighttime ventilation had started outweighed the risks. The EAG did not believe that the company's stopping rule had been adequately justified, and so excluded

it from its base case. At the second committee meeting, the clinical experts explained that they would not support stopping treatment with vamorolone if it was working. They considered that some benefits of vamorolone over other steroid treatments may diminish after puberty has finished, but that the benefit of vamorolone in terms of bone formation would continue throughout a person's lifespan. The patient expert highlighted that if people had good results using vamorolone, they would not be happy to stop using it. The committee noted that there was no clinical justification for a stopping rule to be introduced at nighttime ventilation. It concluded that including a stopping rule at the start of nighttime ventilation was not appropriate.

Dose reductions

3.14 The company's model allowed for dose reductions over time. For prednisone and deflazacort this was informed by CINRG data. For vamorolone, data from the named patient program was used. The EAG noted that the effect of dose reductions was applied differently across treatments in the model. People having prednisone or deflazacort who reduced their dose were assumed to have reduced treatment effects through a change in transition probabilities and reduced side effects. But people who had a dose reduction on vamorolone were assumed to maintain full treatment effects and side effects. The EAG did not think that this approach was plausible. It also noted that this assumption benefitted vamorolone because costs were reduced but benefits remained. The company explained that pharmacological data from phase 1 studies of vamorolone was used to justify the maintained efficacy for vamorolone. It thought that there would be a steep drop in efficacy for prednisone and deflazacort, which it does not expect to happen when the dose of vamorolone is reduced from 6 mg/kg to 4 mg/kg. The committee noted that the company also assumed no reduction in efficacy for people having the 2 mg/kg dose. The clinical experts explained that it is hard to know the benefit of higher doses of corticosteroids. All treatments have a high starting dose, but it is often difficult to maintain this dose because of adverse reactions. So, the dosage will likely be reduced or become intermittent over time. The clinical experts also said that they do not expect the efficacy of vamorolone and other corticosteroids to be different after a dose reduction. Also, they thought that this should have been handled similarly across treatments in the model. At the first committee meeting, the committee

concluded that the company's approach was implausible and that all treatments should have been modelled with reduced effectiveness and adverse events after dose reductions.

In its response to draft guidance, the company maintained that a reduction in dose from 6 mg/kg of vamorolone to 4 mg/kg would not lead to a reduction in clinical effectiveness. It noted that this finding was consistent with the pharmacokinetic-pharmacodynamic analyses of vamorolone. So, in its updated base case, the company used a hazard ratio of 1 (implying no difference in clinical effectiveness) for transitions after dose reduction with vamorolone. The company also included a scenario of a 7% reduction in efficacy from vamorolone 6 mg/kg to vamorolone 4 mg/kg, based on the pharmacokinetic analysis. The company also provided an analysis of reduced doses of prednisone or deflazacort in the phase 3, double-blind FOR-DMD study. It said the analysis showed that people having a reduced dose of prednisone or deflazacort had around twice the risk of losing the ability to stand. It included a hazard ratio of around 2 for transitions after dose reduction for comparator treatments (the company considers the exact number confidential and so it cannot be reported here). The EAG did not think that the company's approach to modelling dose reductions was plausible. It noted that the pharmacokinetic analysis was only based on 1 sample that did not include people having 4 mg/kg of vamorolone. The EAG also noted that this approach might overestimate the progression of disease for patients on prednisone or deflazacort, and the model results were highly sensitive to these assumptions.

To model the impact of dose reduction on adverse events the company took the mean reduction in adverse events after dose reduction in FOR-DMD, which was 18%, and applied it to all of the vamorolone adverse events after dose reduction. For prednisone and deflazacort the company used adverse-event specific reductions from FOR-DMD. The EAG did not consider it appropriate to use a flat reduction of 18% to all adverse events after dose reduction for vamorolone. The EAG noted that it would be more appropriate to apply adverse-event specific changes to the vamorolone arm in the model, as was done for the prednisone and deflazacort treatment arms. The EAG in its base case included no reduction in efficacy or adverse events for any treatments. The committee noted the EAG's concerns with the company's updated analysis. The committee noted that the evidence to suggest there would be a difference in the clinical effectiveness or

adverse-event rates between vamorolone and standard care when reducing the dose was not robust. It also noted that the modelling approach had limitations. It recalled that the clinical experts noted at the first meeting that they do not expect the efficacy of vamorolone and other corticosteroids to be different after a dose reduction. The committee concluded that the best available option was modelling no reduction in efficacy or adverse events for vamorolone and its comparators, although this was still associated with uncertainty.

Utility values

Patient utility values

3.15 Generic preference-based EQ-5D and condition-specific DMD-QoL (DMD-quality of life) data was collected in VISION-DMD. The company explained that the EQ-5D has limited sensitivity to changes in health status in people with DMD. It preferred a condition-specific measure. The company's systematic review identified several studies reporting health-state utilities. The company selected patient utility values from a burden of illness study done as part of Project HERCULES, which used the condition-specific DMD-QoL measure. The patient-reported outcomes from the burden of illness study were applied to all treatment arms in the model. Disutility values because of adverse events were drawn from a number of sources, including previous technology appraisals. The EAG thought that the size of disutilities was broadly reasonable. At the first committee meeting, the committee questioned the face validity of some of the health-state utility values. It was concerned that some values in later, more severe health states were higher than earlier health states, indicating that quality of life improves as the condition progresses. And it did not think this had been fully explained. The EAG noted that the health-state utility values were applied consistently across treatment arms in the model. So, it did not think this had substantially affected the results when the treatments were assumed to be equivalent. In its response to draft guidance, the company updated its source of patient utility data to Landfeldt et al. (2023). The company noted that the values in Landfeldt et al. included a large UK patient sample size and were previously used in NICE's highly specialised technologies guidance on ataluren for treating DMD. The company noted that there were no utility values that were higher in

later, more severe health states. The EAG noted that while 58% of people in the trial were from the US or UK, tariffs from the US were used to convert the responses to an index value. The EAG thought that this might limit generalisability to a UK context. The EAG further highlighted that the Landfeldt et al. health states did not align with the Project HERCULES model. The EAG noted that there were limitations with both sources of utility values and that the impact on the model results was minimal. The committee agreed with the EAG that both sources of utility values had limitations. The committee concluded that uncertainties still remained around the most appropriate source of utility values. The committee preferred to use the utility values from the burden of illness study. This was because they most closely matched the health states in the natural history model, despite the uncertainties.

Carer utility values

3.16 The company included the effects on quality of life for the families and carers of people with DMD. In addition to the burden of illness study, the company also included utility values from Landfeldt et al. (2017). The company's base case used a blend of the Landfeldt et al. (2017) and burden of illness study data for carer disutilities to ensure consistency and face validity. Disutility because of adverse events was only included for carers whose child was having behavioural issues. The committee agreed with the company that DMD is associated with a substantial effect on carers' health-related quality of life. So, including carer quality of life was appropriate. But the committee discussed whether the calculation of the utility decrement was valid and whether it had been applied correctly. The behavioural issues adverse event was reported to last 3 months in the literature. But it was assumed to last for 6 months in the model. This overestimated the effect of behavioural issues on both people with DMD, and their families and carers. The EAG explained that the clinical advice it had been shown suggested that the current assumption of 6 months was not unreasonable. The committee suggested that a monthly QALY loss should have been estimated, to be consistent with the cycle length. The company argued that, because the model only included 1 carer per person and only behavioural issues were considered to affect carer quality of life, its approach was conservative. The patient experts explained that behavioural issues can have a big impact. But the clinical experts explained that behavioural issues can often

subside over time as people get used to the treatment. The committee was aware that behavioural issues accounted for almost all carer quality-of-life gains, so it was important that the model captures this aspect appropriately. The committee considered that carer quality of life was appropriate to include and, because it was a major driver of QALYs, it should have been modelled appropriately. At the first meeting the committee was not convinced that carer health-related quality of life had been modelled robustly, so it said that more analyses are needed. In response to draft guidance the company updated its approach to modelling behavioural issues (see section 3.17). At the second committee meeting the committee discussed the appropriate number of carers to include in the model. The patient expert explained that many people with DMD would have 2 carers. They explained that people with DMD often need 24-hour care, which would be impossible for 1 carer. The committee concluded that the company's assumption of including 2 carers for non-ambulatory health states was also appropriate.

Modelling behavioural issues

3.17 In response to draft guidance the company revised its base case, to increase the duration of behavioural issues in the model from 6 to 18 months. The company noted that this was based on clinical expert opinion that the duration of behavioural issues could last up to 2 years. The company assumed that the behavioural issues were equal in severity to severe side effects from anti-epileptic medicines, and applied a decrement of 0.12 per year from a study of the side effects in anti-epileptic medicines. The EAG's clinical expert agreed with the company's updated length of the behavioural issues decrement. But the clinical expert advised the EAG that corticosteroids would only cause behavioural issues until age 12. So, the EAG's base case only applied the behavioural issues adverse-event decrement in the model until people were age 12. The EAG was also concerned about the company's choice of utility decrement for behavioural issues. It noted that the source of the decrement was from a study of the side effects in anti-epileptic medicines. The EAG noted that the disutility of 0.12 per year may overestimate the impact of behavioural issues from corticosteroids and preferred using a disutility equal to moderate behavioural issues from corticosteroids (0.06 per year). The committee discussed the results from a patient survey submitted by a patient organisation in response to the draft

guidance consultation. The survey collected qualitative and quantitative data from 76 people with DMD and carers on their experiences and the impact of side effects associated with corticosteroid use. The results showed that the critical adverse events for people with DMD and their carers were:

- stunted growth
- behaviour problems
- weight gain
- risk of fractures and osteoporosis.

This was reflected in the relative disutilities for adverse events. The EAG noted that the survey highlights that the frequency of behavioural issues is variable. It noted that 61.1% of people experienced behavioural issues either 'often' or 'all the time'. The remaining 39.9% experienced it only 'some of the time', 'rarely' or chose 'not applicable' (assumed to be 'not at all'). The EAG noted that this variability is not captured by the company modelling and that the EAG approach (applying behavioural issues only for people aged 4 to 12) partially accounts for this. At the second committee meeting, the clinical experts explained that many people with DMD have a specific cognitive profile, which impacts how corticosteroids affect their behaviour. They explained that by age 12, behavioural issues in people with DMD would be better understood and managed by carers, but behavioural issues would still be present. The clinical experts did not think that the EAG's assumption that behavioural issues would only be caused by corticosteroids until age 12 was plausible. The committee noted the concerns from clinical experts about the EAG's assumptions. So, the committee concluded that it preferred the company's assumption of a disutility of 0.12 per year over 18 months for behavioural issues, which applied to all ages.

Costs

Resource use

3.18 The company included drug, health-state and adverse-event costs in its model.

The model captured the weight-based dosing of vamorolone, up to 240 mg for people weighing 40 kg or more. The committee noted that the increased treatment costs because of weight increased the impact of the assumptions around treatment discontinuation (see section 3.12). The company assigned resource use associated with adverse events based on assumed contact with the NHS. Costs by health state were extracted from the burden of illness study. NICE's manual on health technology evaluations specifies that costs should be from an NHS and personal social services perspective only. But the company included some health-state costs in its base case that were outside of the reference case. These costs included out-of-pocket costs (that is, for over-the-counter medicines, transport, and alternative and complementary therapies) and transfer payments. The company also included costs related to growth hormones. The EAG explained that growth hormones are rarely used in the UK. The committee concluded at the first meeting that out-of-scope and growth-hormone costs should have been excluded. In its response to draft guidance, the company excluded out-of-scope costs. The company also changed its source of health-state costs to Landfeldt et al. (2017). The company noted that this was consistent with NICE's highly specialised technology guidance on ataluren for treating DMD. The EAG highlighted that the health states in Landfeldt et al. (2017) did not align with the health states in the Project HERCULES model. It did not believe there was justification for changing the source of health-state costs. The committee noted that Landfeldt et al. (2017) was an international study, meaning that costs in other countries were included in the figures. The clinical experts advised that there is a standard of treatment for DMD that would be followed by all the countries included in Landfeldt et al. (2017). The committee noted that the burden of illness costs reflected the health states from the Project HERCULES model. The committee believed there was not sufficient justification from the company for switching the costs to Landfeldt et al. (2017). The committee understood that previous NICE guidance on DMD had used the Landfeldt et al. (2017) costs but thought that that should not determine what is relevant to this evaluation. The committee noted that the Landfeldt et al. (2017) costs were much higher for each health sate than the burden of illness study. It was also unclear whether they were all from the perspective of the NHS and personal social services. The committee acknowledged that the burden of illness study was consistent with the Project HERCULES model. It did not see convincing evidence to change the source of costs to Landfeldt et al. (2017). So, the committee concluded that it preferred to use the burden of illness study to inform costs in

the model.

Severity

3.19 The committee discussed the severity of the condition (the future health lost by people living with DMD and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's manual on health technology evaluations. The company assumed a starting age of 4 years, the earliest permitted age in vamorolone's marketing authorisation. The company's original base case predicted an absolute shortfall of 18.02 and a proportional shortfall of 0.72, and applied a severity weight of 1.7 to QALYs. The EAG thought the company's estimate was highly uncertain, and noted that it had a substantial impact on the cost-effectiveness results. It explained that the company used a generic preference-based utility instrument to derive general population QALYs, but a condition-specific measure to generate QALYs for people with DMD having standard care. The company's base-case economic model applied the severity modifier to both patient and carer QALYs. The EAG corrected this by only applying the modifier to patient QALYs. The committee concluded that the QALY weighting should have been applied to patient QALYs only. The EAG's base case estimated an absolute shortfall of 17.62 and a proportional shortfall of 0.71, implying a severity weight of 1.2. The committee understood that the modelling of dose reductions affected the QALY shortfall between the company's and EAG's base cases (see section 3.14). The committee noted that this difference in dose reduction assumptions increased the QALY estimates for standard care in the EAG's base case, so may have underestimated the absolute shortfall. The committee acknowledged the EAG's concerns around uncertainty. It recalled that the natural history model data used to calculate standard-care survival was likely overestimated (see section 3.9), which it considered would have underestimated the absolute shortfall. The committee also acknowledged that the severity calculations were sensitive to treatment starting age. But it accepted clinical expert opinion that treatment would be started as soon as possible in DMD. The committee concluded that a severity weight of 1.7 was appropriate. At the second meeting, the committee noted that the QALY shortfall had changed because of the new analysis. But it concluded that a severity weight

of 1.7 was still appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.20 NICE's manual on health technology evaluation notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The manual also states that decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider the degree of certainty and uncertainty around the ICER, and aspects that relate to uncaptured benefits and non-health factors. The committee discussed the certainty around the ICER. It recalled that at the first committee meeting it had considered that a threshold of £30,000 would be acceptable. But it also recalled that it could not establish a preferred ICER and requested further evidence from the company. The committee noted that after seeing the further evidence that had been requested at the first committee meeting there was still considerable unresolved uncertainty. This included:

- a lack of treatment sequencing in the modelling (see section 3.4)
- no evidence of equivalence with prednisone (see section 3.6)
- long-term muscle-function assumptions (see section 3.10)
- adverse-event assumptions (see section 3.11)
- outcomes after dose reduction (see section 3.14)
- the natural history model (see section 3.9)
- utility value and resource use assumptions (see section 3.15).

The committee discussed uncaptured benefits and non-health factors. It noted that it did not identify any additional benefits of vamorolone that were

not already captured in the economic modelling (see section 3.23). The committee was aware that it may accept a higher degree of uncertainty when evidence generation is difficult, and considered how the nature of the condition affected the ability to generate high-quality evidence. It noted in particular that the condition is rare and affects children. It acknowledged that several of the key uncertainties were affected by the rarity of DMD, including the muscle-function outcomes, and adverse-event outcomes after stopping treatment. But it noted that there was an unusually high level of uncertainty even when considering the rarity of the condition. It recalled that the manual states that as the ICER for a technology increases in the range of £20,000 to £30,000 per QALY gained, the committee's decisions about the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed (the degree of certainty and uncertainty around the ICER and aspects that relate to uncaptured benefits and non-health factors). So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Committee's preferred assumptions

3.21 The committee recalled its preferred assumptions, which were:

- having no decrement for long-term extrapolation of muscle function (see section 3.10)
- applying a disutility of 0.12 per year for behavioural issues over 18 months applied to all ages (see section 3.17)
- removing the stopping rule for nighttime ventilation (see section 3.13)
- using the same dose-reduction assumptions for vamorolone and standard care (see section 3.14)
- using the burden of illness study for patient utility values (see section 3.15)
- including 2 carers for carer utility decrements (see section 3.16)
- using the burden of illness study for costs (see section 3.18).

Because there is a confidential discount for vamorolone, the exact ICERs cannot be reported here. The committee considered the cost-effectiveness results when using its preferred assumptions. The ICER for vamorolone compared with standard care was within the range NICE considers a cost-effective use of NHS resources. So, the committee concluded that vamorolone could be recommended for routine use for treating DMD in people 4 years and over.

Equality

3.22 The committee noted that DMD affects both children and young adults. Age is protected under the Equality Act 2010. But, because its recommendation does not restrict access to treatment for some people over others, the committee agreed that this was not a potential equality issue. Some stakeholders said it was important that people with DMD did not have to travel excessive distances for treatment, given that DMD causes reduced mobility. The committee acknowledged that clinical expertise would usually be concentrated at a small number of centres. In response to draft guidance a stakeholder noted that a significant proportion of the DMD population had learning disabilities, attention deficit hyperactivity disorder (ADHD), autism or pre-existing psychiatric difficulties. They noted that this group may be more likely to experience behavioural issues and may be more likely to stop corticosteroid treatment. This would result in people with these conditions not having any suitable treatment options. The committee heard from the clinical experts who noted that behavioural issues are linked to a diagnosis of DMD, which can manifest in different ways in different children. The experts noted that having behavioural problems is not a contraindication for corticosteroid use. The committee noted that there is some evidence that behavioural issues linked to ADHD, autism, learning disabilities or pre-existing psychiatric difficulties are not exacerbated by steroid use. The clinical experts noted that there are very few people in clinical practice who are unable to tolerate any dose of steroid. The committee recalled its discussion on treatment sequencing (see section 3.4). It was satisfied that any recommendation would not discriminate against people who could not have corticosteroids or who have learning disabilities, ADHD, autism or pre-existing

psychiatric difficulties. No other potential equality issues were identified by the committee.

Other factors

3.23 The committee discussed whether vamorolone is innovative. It did not identify additional benefits of vamorolone that were not already captured in the economic modelling. The company highlighted that societal costs are important because of the substantial burden faced by people with DMD, and their families and carers. It explained that caring for people with DMD is time consuming and has a severe negative impact on several aspects of daily living, including productivity. The committee agreed to include the impact of DMD on health-related quality of life for carers in its preferred assumptions (see section 3.16). The committee also concluded that NICE's manual on health technology evaluations specifies that costs should be from an NHS and personal social services perspective only. So, the committee concluded that all the benefits of vamorolone had already been taken into account.

Conclusion

Recommendation

3.24 The committee concluded that vamorolone is an effective treatment for DMD, but its relative effectiveness compared with other corticosteroids was highly uncertain. It considered that vamorolone could offer important benefits because of its potential to reduce side effects associated with corticosteroids. The patients and clinical experts explained that there is a high unmet need in this disease area. The committee also considered the severity of DMD and applied the 1.7 severity weighting to QALYs. It concluded that the most plausible ICER is within the range NICE considers a cost-effective use of NHS resources. The committee concluded that vamorolone was a cost-effective treatment option. So, vamorolone is recommended for treating DMD in people 4 years and over.

4 Implementation

4.1 Section 7 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 evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal 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 draft guidance.

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 a patient has Duchenne muscular dystrophy and the healthcare professional responsible for their care thinks that vamorolone 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 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered 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

Richard Nicholas
Vice chair, technology appraisal committee C

NICE project team

Each 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.

Lewis Ralph and George Millington
Technical leads

Alan Moore and Victoria Kelly
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