NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using vamorolone in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: March 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using vamorolone in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 24 April 2024
- Second evaluation committee meeting: 07 May 2024
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Vamorolone is not recommended, within its marketing authorisation, for treating Duchenne muscular dystrophy (DMD) in people 4 years and over.

1.2 This recommendation is not intended to affect treatment with vamorolone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

Current treatment options for DMD are limited, and there is an unmet need for new treatments. Corticosteroids, specifically prednisone, prednisolone or deflazacort, are used to slow progression of the condition.

Evidence from a clinical trial shows that vamorolone improves muscle function outcomes compared with placebo. But the trial only included a small number of people and was short. So, compared with prednisone, it is uncertain whether vamorolone is similar at improving muscle function outcomes, and how well it works in the long term. The evidence suggests that vamorolone is likely to reduce the number of side effects compared with prednisone, but to what extent is uncertain. Also, the trial only included people who had not started treatment for DMD. So, it is uncertain how well vamorolone works for people who have had corticosteroids. There are no comparisons with other corticosteroids.

Because of the uncertainties in the clinical evidence and economic model, it is not possible to determine the most likely cost-effectiveness estimates for vamorolone. So, further modelling is needed, and vamorolone is not recommended.

2 Information about vamorolone

Marketing authorisation indication

2.1 Vamorolone (Agamree, Santhera) is indicated for '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, which would have applied if vamorolone had been recommended.

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 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, it 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 and 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, care is taken to monitor their spines, sleep-disordered breathing and heart. 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 they become 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 both 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 treat symptoms involved with the progression of DMD. They have been shown to have significant benefits in:

- slowing the progressive loss of muscular strength
- extending the ability to walk independently
- avoiding 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 that 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 also 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 committee concluded that current treatment options are limited and have substantial side effects, so there is a need for new treatments with fewer side effects. The patient experts detailed how all respondents in a recent survey reported disadvantages for currently available corticosteroids. While all respondents acknowledged the benefits of these treatments in terms of slowing progression and improving prognosis, they would welcome treatment options with less severe side effects. The committee concluded there is a need for effective treatments for DMD with less 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 be treated 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 that would want to switch to vamorolone for its anticipated better safety profile. The committee heard that vamorolone was expected to provide important benefits for people with DMD. The committee concluded that vamorolone would be likely to be used for people who

have not had treatment for DMD. It and acknowledged there was also interest in vamorolone for people who have had corticosteroid treatment.

Clinical effectiveness

VISION-DMD trial

3.5 The clinical-effectiveness evidence for vamorolone was mainly 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 0.75mg/kg/day or placebo. The primary outcome in the trial was time to stand. Other muscle function outcomes included the 6-minute walking 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 clinical experts comment that the earlier treatment is started the better and that, if treatment is started after 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 were 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 people who have had corticosteroid treatment were not captured in the evidence.

Muscle function outcomes

3.6 After 24 weeks, there was a clinically meaningful improved 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 stated that these numerical differences were not statistically significant. It concluded that the 2 treatments could be considered equivalent. The EAG did not consider 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 stated 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. The committee concluded that vamorolone

improved outcomes compared with placebo. But it did not think there was 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 only considering moderate to severe adverse events, there were no incidences of weight gain, behavioural or immune-related issues, or gastrointestinal, skin or hair events with vamorolone over 24 weeks. But, with prednisone, there were low rates of weight gain, and gastrointestinal and skin or hair 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 these assumptions, 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 VISION-DMD follow up 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, 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 UK-led project initiated 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 night-time 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 there was no clinical-effectiveness evidence for treated DMD. 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, so they all followed the natural history model. 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 section 3.3 and section 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 consider the company's approach to modelling a comparison against a blended standard-care arm to be 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.

Natural history model

3.9 The committee noted that the project HERCULES natural history data was likely the best available model. 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 concluded that the model may have overestimated life expectancy for DMD.

Assumptions

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 concluded 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 concluded that it would also want to see a scenario that assumed a

difference in muscle function outcomes between treatments based on VISION-DMD.

Modelling of 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 the 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 how the rate 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 QALYs gains for vamorolone in the model

(see section 3.15). 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. The committee concluded that the modelling of adverse events for vamorolone was highly uncertain, given the definition used and the short trial duration. 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.

Stopping treatment

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 considered 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 stated that the EAG's approach of using deflazacort as a proxy led to an overestimation for time on treatment with vamorolone. The company considered that, because prednisone data was the most mature, it might have been more appropriate to use it 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 how 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 company noted the possibility of a treatment stopping rule for vamorolone. But it did not provide any further details on the clinical rationale for this, criteria on which it could be based or on its appropriateness in practice. So, the committee could not consider any stopping rule. 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 that the company's modelling of stopping treatment was not suitable for decision

making. It considered that the EAG's assumptions were preferable, but still highly uncertain. It also concluded that further modelling of stopping treatment was needed.

Dose reductions

3.13 The company's model allowed for dose reductions over time. For standard-care treatments this was informed by CINRG data. For vamorolone, data from the named patient programme was used. The EAG noted that the effect of dose reductions was applied differently across treatments in the model. People on standard care 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 consider this approach to be 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 drops from 6 mg to 4 mg. The committee noted that the company also assumed no reduction in efficacy for people having the 2 mg 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 stated that they do not expect vamorolone and other corticosteroids efficacy to be different after a dose reduction. Also, they thought that this should have been handled similarly across treatments in the model. The EAG explored a scenario in which the benefits of standard-care treatments were maintained after dose reduction, to match the assumption for vamorolone. The EAG acknowledged that it would have preferred to have reduced the effect for vamorolone to match

standard care instead. But it said that this was not possible with the current model. The committee concluded that the company's approach was implausible and that all treatments should have been modelled the same in terms of their effectiveness and tolerability after dose reductions. The committee also concluded that it would like to see an additional scenario in which the benefits are reduced after dose reduction in all treatment arms.

Utility values

Patient utility values

3.14 Generic preference-based EQ-5D and condition-specific DMD-QoL 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 considered the size of disutilities to be broadly reasonable. 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. But it did not think this had not 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. The committee noted concerns with the face validity of the application of adverse event disutilities. The committee asked whether the application of disutility for behavioural issues had been properly applied in the model. It

suggested that a monthly QALY loss should have been estimated to be consistent with the cycle length. It also highlighted that any assumed difference in treatment effect between vamorolone and standard-care treatments would have created differences in the time spent and QALYs accrued in each health state for each arm. So, the validity of health-state utilities would become important if the assumption of equivalence was not accepted. The committee concluded that, when modelling plausible treatment-effectiveness scenarios, care is needed to ensure the health-state utility values and adverse event disutilities are plausible and robust.

Carer utility values

3.15 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. and burden of illness studies 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 asked whether the impact of behavioural issues was overestimated in the company's model. This was because people with DMD, and their families and carers saw large decrements at a constant rate for long periods of time. As with patient disutilities, the committee asked whether the application of a disutility for behavioural issues was being properly applied in the model. It 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. The clinical experts explained that behavioural issues can often subside over time as people get used to 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. The committee was not convinced that carer health-related quality of life had been modelled robustly, so said that more analyses are needed.

Costs

Resource use

3.16 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 stopping treatment (see section 3.12). The company assigned resource use associated with adverse events based on assumed contact with the health service. Costs by health state were extracted from the burden of illness study. The NICE's manual on health technology evaluation 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 that out-of-scope and growth-hormone costs should have been excluded.

Severity

3.17 The committee considered 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 evaluation. The company assumed a starting age of 4 years, the earliest permitted age in vamorolone's marketing authorisation. The company's 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 subject to high uncertainty, 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 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 concluded that the QALY weighting should have been applied to patient QALYs only. The committee understood that the modelling of dose reductions affected the QALY shortfall between the company's and EAG's base cases (see section 3.13). 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.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.18 Because there is a confidential discount for vamorolone, the exact incremental cost-effectiveness ratios (ICERs) cannot be reported here. The committee considered the cost-effectiveness results when using the company's and EAG's base cases. The committee was also presented with a range of scenarios investigating the impact of different assumptions. The cost-effectiveness estimates in the company's corrected base case were above what NICE normally considers an acceptable use of NHS resources. The EAG made several changes to the company's base case. These changes further increased cost-effectiveness estimates, which were still above what NICE normally considers an acceptable use of NHS resources.

Acceptable ICER

3.19 NICE's manual on health technology evaluation notes that, above a most plausible 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 committee was aware that it may accept a higher degree of uncertainty when evidence generation is particularly difficult because the condition is rare. It noted that several of the key uncertainties were affected by the rarity of DMD, including the muscle function, adverse event and outcomes after stopping treatment. So, the committee concluded that an acceptable ICER would be towards the

upper end of the range NICE considers a cost-effective use of NHS resources (around £30,000 per QALY gained).

Committee's preferred assumptions

3.20 The committee recalled its conclusion that the company's modelling was unreliable in several key areas, including:

- long-term extrapolation of muscle function (see section 3.10)
- outcomes after stopping treatment (see section 3.12)
- dose reduction assumptions (see section 3.13)
- health-related quality-of-life assumptions (see section 3.14 and section 3.15).

So, it so concluded that it was not possible to establish a plausible cost-effectiveness estimate. It also concluded that it needed further economic modelling analysis. The committee considered that further modelling should reflect its preferred assumptions, including:

- considering prednisone and deflazacort as individual comparators in a fully incremental analysis (see section 3.8).
- considering a difference in muscle function outcomes between treatments based on VISION-DMD (see section 3.10).
- plausible assumptions for stopping treatment with vamorolone (see section 3.12).
- plausible assumptions after dose reduction when considering no difference between vamorolone and prednisone or deflazacort (see section 3.13).
- excluding growth-hormone and non-reference case costs (see section 3.16).
- using a QALY weight of 1.7 applied to patient QALYs only (see section 3.17).

The committee outlined the additional analysis that it would like to receive from the company during consultation:

- a scenario in which dose reductions lead to reduced efficacy applied consistently to each treatment (see section 3.13).
- additional analysis around stopping each treatment in the model, including a scenario in which vamorolone is associated with a longer time on treatment, to reflect the likely improved safely profile of vamorolone compared with standard care (see section 3.12).
- more robust modelling of adverse events, including the severity of adverse events, how behavioural issues are modelled and the impact of adverse events over time (see section 3.11).
- more robust modelling of health-related quality of life, including health-state utility values, and patient and carer adverse event disutilities (see section 3.14 and section 3.15).
- updating the economic model to account for the potential of treatment sequencing, to reflect the treatment pathway for DMD (see section 3.8).

Managed access

3.21 The committee noted that no proposal for managed access had been submitted by the company. It acknowledged that, in principle, there may be uncertainties that could be addressed by additional evidence. But, because there was no submission from the company, it was not able to consider managed access.

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 equalities 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. No other potential equality issues were identified by the committee.

Other factors

3.23 The committee considered whether vamorolone is innovative. It did not identify additional benefits of vamorolone that were not already captured in the economic modelling. The company highlighted 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 carers health-related quality of life in its preferred assumptions (see section 3.15). The committee also concluded that NICE's manual on health technology evaluation specifies 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 adverse events 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 it was not possible to establish a plausible ICER, so further modelling is needed. The committee concluded that there was not enough evidence to conclude that vamorolone is a cost-effective treatment option. So, it did not recommend vamorolone for treating DMD in people 4 years and over.

4 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

Technical lead

Alan Moore

Technical adviser

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Project manager

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