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SMC2721

vamorolone oral suspension (Agamree®)

Santhera Pharmaceuticals (Deutschland) GmbH

06 December 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

vamorolone (Agamree®) is accepted for use within NHSScotland.

Indication under review: treatment of Duchenne muscular dystrophy (DMD) in patients aged 4 years and older.

In a randomised, double-blind, phase IIb study, treatment with vamorolone resulted in a significant improvement in the change in time to stand from supine (TTSTAND) velocity and change in 6-minute walk test (6MWT) distance between baseline and week 24, compared with placebo.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Vamorolone is a synthetic corticosteroid analogue that selectively binds to the glucocorticoid receptor and also inhibits the activation of the mineralocorticoid receptor by aldosterone. The specific structure of vamorolone means that it is unlikely to be a substrate for 11β-hydroxysteroid dehydrogenases, whose enzymatic activities have been linked to adverse effects associated with glucocorticoid therapy (for example muscle atrophy, bone loss, hypertension, and weight gain). The exact mechanism that vamorolone exerts its therapeutic effects in patients with Duchenne Muscular Dystrophy (DMD) is unknown.[1, 2]

The recommended dose of vamorolone is 6 mg/kg once daily in patients weighing less than 40 kg. In patients weighing 40 kg and above, the recommended dose is 240 mg once daily. The daily dose may be down-titrated to 4 mg/kg/day or 2 mg/kg/day based on individual tolerability. Patients should be maintained at the highest tolerated dose within the dose range. See Summary of Product Characteristics (SPC) for more details.[1]

1.2. Disease background

DMD is a rare, severe X-linked recessive genetic condition that causes muscle weakness leading to progressive disability and early death due to respiratory or cardiac failure. This condition is caused by a mutation in the gene that codes for dystrophin, a protein important for the strength, stability and function of muscle cells. DMD predominantly affects males, carrier females can become symptomatic, although this is rare. Children with DMD experience a decline in muscle strength from as young as 2 years old and over times this leads to being unable to walk and losing arm and hand function. Patients will usually require ventilatory assistance by their late teens.[2-4] 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 approximately 30 years.[5] It is estimated that there are approximately 2,500 people in the UK living with DMD, and approximately 80 to 100 children with DMD in NHS Scotland.[6-8]

1.3. Treatment pathway and relevant comparators

There are currently no curative treatments available for DMD. Treatment is based on the prevention and management of complications (for example joint contractures, scoliosis, bone fractures, cardiomyopathy, and respiratory insufficiency) and includes the use of physiotherapy and corticosteroids; both should be continued after loss of ambulation according to current guideline recommendations.[2, 3]

Corticosteroids (specifically prednisolone and deflazacort) are the only treatments that have been shown to temporarily reduce motor function decline.[2, 3] However, some patients may not be able to take corticosteroids due to lack of response or adverse events. Complications of corticosteroids include: osteoporosis, reduced bone strength and density, increased risk of spinal fractures, weight gain, negative behaviour changes, growth restriction, and delayed puberty.[2, 3]

SMC has completed its initial assessment of the evidence for ataluren for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older (SMC2327).

1.4. Category for decision-making process

Eligibility for a PACE meeting

Vamorolone meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The evidence to support the use of vamorolone comes from the VISION-DMD study. Details are summarised in table 2.1.

Table 2.1. Overview of relevant studies

Criteria	VISION-DMD[2, 9]
Study design	International, randomised, double-blind, parallel group, phase IIb study.
Eligible patients	• Patients aged 4 to < 7 years of age (at screening) with a confirmed diagnosis of DMD. • No current or prior treatment with oral corticosteroids. • Body weight > 13.0 kg and ≤ 39.9 kg at screening. • Able to walk independently (ambulatory) without assistive devices at screening. • Able to complete the time to stand from supine (TTSTAND) in less than 10 seconds without assistance at screening.
Treatments & Randomisation	For the double-blind RCT phase (weeks 0 to 24) of the study (period 1), patients were randomised equally to receive oral: • vamorolone 2.0 mg/kg/day • vamorolone 6.0 mg/kg/day • prednisone 0.75 mg/kg/day • placebo To maintain the double-blinding in this treatment period, all subjects received either a matching placebo for vamorolone (that is a placebo oral suspension), a matching placebo for prednisone (that is a placebo tablet) or both (that is placebo oral suspension and placebo tablet). All patients remaining in the study then entered a transition period (weeks 25 to 28) during which vamorolone or its matching placebo were administered at the same dose as in period 1, but the dose of prednisone and its matching placebo tablet were tapered to zero. Patients then entered the 20-week treatment extension phase (weeks 29 to 48), period 2. All patients previously treated with prednisone or placebo (in period 1) were randomised equally to receive vamorolone 2.0 mg/kg/day or 6.0 mg/kg/day. Patients who received vamorolone in period 1 continued the same vamorolone dose they were originally randomised to. Patients were permitted hydrocortisone or prednisone stress dosing during an illness, injury, or surgical procedure to avoid an adrenal crisis. Randomisation was stratified according to age at study entry (<6 years and ≥6 years).
Primary outcome	Change from baseline to Week 24 in TTSTAND velocity, for vamorolone 6.0 mg/kg/day compared to placebo. TTSTAND is a linear measurement expressed as the number of seconds taken to rise from a supine position without assistance. The TTSTAND declines rapidly over time in patients with DMD and has

	been previously shown to be an early prognostic factor for disease progression and loss of ambulation. TTSTAND velocity is a conversion of TTSTAND.
Secondary & exploratory outcomes	<u>Secondary outcomes in pre-specified hierarchical order</u> Change from baseline to week 24 in: • TTSTAND velocity for vamorolone 2 mg/kg/day versus placebo. • 6MWT distance for vamorolone 6 mg/kg/day versus placebo. • 6MWT distance for vamorolone 2 mg/kg/day versus placebo. • TTRW velocity for vamorolone 6 mg/kg/day versus placebo. • TTRW velocity for vamorolone 2 mg/kg/day versus placebo. • 6MWT distance for vamorolone 6 mg/kg/day versus prednisone. • 6MWT distance for vamorolone 2 mg/kg/day versus prednisone. <u>Other secondary outcomes (comparing each vamorolone dose with placebo or prednisone)</u> Change from baseline to week 24 in: • change from baseline in TTCLIMB velocity • change from baseline in NSAA score • change from baseline in knee extension muscle strength • change from baseline in elbow extension muscle strength 6MWT assesses distance walked over 6 minutes as a sub-maximal test of aerobic capacity/endurance. TTRW is conducted as part of the NSAA; the NSAA is a 17-item rating scale that is used to measure functional motor abilities in ambulant children with DMD. It is usually used to monitor the progression of the disease and treatment effects. It uses a scale of 0 (unable), 1 (completed independently but with modifications), or 2 (completed without compensation) for a total score ranging from 0 to 34 (higher score indicates greater functional ability). The higher the total score, the more mobile the patient is. Repeat NSAA tests performed over time can be used to compare changes in physical disease progression. Muscle strength was assessed in the exploratory outcomes: change from baseline in knee extension muscle strength and change from baseline in elbow flexor muscle strength.
Statistical analysis	The predefined primary efficacy analysis was conducted on the mITT-1 population (all randomised patients who received at least one dose of study medication during period 1 and had at least one post-baseline efficacy assessment during Period 1) with multiple imputation based on the missing at random imputation as per the European regulator analysis. A hierarchical statistical testing strategy was applied in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The hierarchical order of testing was the primary outcome followed by the secondary outcomes in the order outlined above.

Abbreviations: 6MWT = 6-minute walk test; DMD = Duchenne muscular dystrophy; mITT = modified intent-to-treat; NSAA = North Star Ambulatory Assessment; TTCLIMB = time to climb 4 stairs; TTRW = Time to run or walk 10 metres; TTSTAND = time to stand from supine.

Results for the primary and selected secondary outcomes are presented in Table 2.2. The most relevant results are for the group who received 6 mg/kg/day, the licensed dose for patients weighing < 40kg. At the primary analysis treatment with vamorolone 6 mg/kg/day resulted in statistically significant improvements in time to stand from supine (TTSTAND) velocity, assessed as the primary outcome, and in 6-minute walk test (6MWT) distance, and time to run or walk 10 metres (TTRW) velocity compared with placebo.[2, 9] The study was not designed to detect statistical differences between vamorolone and prednisone however improvements seen with vamorolone 6 mg/kg in TTSTAND, TTRW and TTCLIMB velocity were similar to those seen with prednisone at Week 24; while for the 6MWT and the NSAA score prednisone resulted in numerically better results.[2] Measures of muscle strength (change from baseline to week 24 in knee extension and

elbow flexor muscle strength) indicated improvements in the vamorolone 6mg/kg/day group compared to placebo. However, whilst muscle strength significantly improved in the prednisone group, it only slightly improved in the vamorolone groups.[2] For vamorolone 6 mg/kg/day, the improvements in all tested measurements of lower limb function seen at 24 weeks were largely maintained for 48 weeks of treatment.[1]

Table 2.2: Primary and selected secondary outcomes from the VISION-DMD study at week 24 in the modified intention-to-treat-1 (mITT-1) population.[2, 9]

	Vamorolone 6 mg/kg/day (n=28)	Vamorolone 2 mg/kg/day (n=30)	Prednisone 0.75 mg/kg/day (n=31)	Placebo (n=28)
Change from baseline to week 24 in TTSTAND velocity (rises/second)				
Baseline, mean (SD)	0.19 (0.06)	0.18 (0.05)	0.22 (0.06)	0.20 (0.06)
Week 24, mean (SD)	0.24 (0.08)	0.23 (0.09)	0.29 (0.09)	0.19 (0.09)
LSM change from baseline at week 24 (SE)	0.05 (0.01)	0.03 (0.01)	0.07 (0.01)	-0.01 (0.01)
LSM difference versus placebo (95% CI), p-value	0.06 (0.02 to 0.10), p=0.002	0.04 (0.01 to 0.08), p=0.02	Not given[1]	-
LSM difference versus prednisone (95% CI)	-0.02 (-0.06 to 0.02)	-0.03 (-0.07 to 0.00)	-	Not reported
Change from baseline to week 24 in 6MWT distance (metres)				
Baseline, mean (SD)	312.5 (56.2)	316.1 (58.4)	343.3 (55.8)	354.5 (77.6)
Week 24, mean (SD)	355.9 (50.9)	349.1 (66.0)	395.5 (57.3)	339.0 (60.9)
LSM change from baseline at week 24 (SE)	24.6 (10.1)	25.0 (10.0)	44.1 (9.6)	-11.4 (10.6)
LSM difference versus placebo (95% CI), p-value	35.9 (8.0 to 63.9), p=0.01	36.3 (8.3 to 64.4), p=0.01	Not given[1]	-
LSM difference versus prednisone (95% CI)	-19.6 (-45.8 to 6.7)[a]	-19.1 (-46.2 to 7.9)[a]	-	Not reported
Change from baseline to week 24 in TTRW velocity (metres/second)				
Baseline, mean (SD)	1.60 (0.40)	1.56 (0.29)	1.90 (0.43)	1.74 (0.35)
Week 24, mean (SD)	1.89 (0.41)	1.72 (0.37)	2.25 (0.43)	1.77 (0.44)
LSM change from baseline at week 24 (SE)	0.25 (0.06)	0.14 (0.06)	0.37 (0.05)	0.01 (0.06)
LSM difference versus placebo (95% CI), p-value	0.24 (0.09 to 0.39), p=0.002	0.13 (-0.03 to 0.28), NSS	Not given[1]	-
LSM difference versus prednisone (95% CI)	Not reported	Not reported	-	Not reported

[a] Since the comparison of TTRW velocity for vamorolone 2 mg/kg/day versus placebo was not statistically significant, no formal statistical testing of 6MWT distance for vamorolone 6 mg/kg and 2 mg/kg vs prednisone was possible.

Abbreviations: 6MWT = 6-minute walk test; CI = confidence interval; DMD = Duchenne muscular dystrophy; LSM = least squares mean; mITT = modified intent-to-treat; NSAA = North Star Ambulatory Assessment; NSS = not statistically significant; SD = standard deviation; SE = standard error; TTRW = time to run or walk 10 metres; TTSTAND = time to stand from supine.

2.2. Health-related quality of life (QoL) outcomes

Patient-reported outcomes were assessed in VISION-DMD using the Paediatric Outcomes Data Collection Instrument (PODCI), which assessed physical functioning; Psychosocial Adjustment and Role Skills Scale III (PARS III), and Treatment Satisfaction Questionnaire (TSQM).[2, 9] These outcomes were not used in the economic analysis. Generally, no differences were observed between both vamorolone dose groups and the placebo group.[9] However, the PARS III questionnaire suggested that vamorolone 2 mg/kg/day showed better adjustment for anxiety and depression compared with prednisone however, this was not adjusted for multiple testing.

2.3. Supportive studies

VBP15-LTE was an international, open-label, parallel group, phase II 24-month extension study to assess the long-term efficacy and safety of vamorolone. 46 patients were enrolled who had been previously treated with vamorolone for 6 months in VBP15-002 (2 weeks treatment) and VBP15-003 (24 weeks 'treatment), and so the combined treatment duration during VBP15-002, VBP15-003, and VBP15-LTE was 30 months. Overall, the improvements in TTSTAND, TTRW and TTCLIMB velocity, and 6MWT distance seen with both vamorolone dose groups at Week 24 in Study VBP15-003 were maintained up to month 18 in Study VBP15-LTE, but this was followed by a gradual decline towards baseline after month 18.[2, 10] However, data from historical cohorts of patients with DMD who have received corticosteroids for 30 months appear to show a similar efficacy pattern.[10]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

As per the instruction of the European regulator, the submitting company conducted a patient level matched comparison of both vamorolone doses with prednisone and deflazacort. The aim was to provide efficacy and safety comparisons beyond 24 weeks, and to assess whether the efficacy profile of the two vamorolone doses is comparable to prednisone or deflazacort. [2] See Table 2.3 for details.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Patient level matched comparison where patients were matched in a two-step process. Firstly, based on inclusion criteria including confirmed DMD, between 4 and < 7 years of age at baseline, able to walk independently, and able to complete time to stand from supine (TTSTAND) without assistance. Secondly, propensity scores were calculated using logistic regression accounting for factors known to predict DMD disease progression and severity which included: age; TTSTAND velocity; North Star Ambulatory Assessment (NSAA) score; baseline weight and height (z-scores).
Population	Boys aged 4 to < 7 years of age with DMD, that were corticosteroid naïve.
Comparators (studies included)	Vamorolone 2 mg/kg/day and 6 mg/kg/day (VISION-DMD)[9, 11] compared with: prednisone 0.75 mg/kg/day (FOR-DMD)[12] and deflazacort 0.9 mg/kg/day (FOR-DMD).[12]
Outcomes	Efficacy outcomes: TTSTAND velocity; 6MWT distance; TTRW velocity; NSAA score. Safety outcomes: Height, weight, adverse events. Assessed at: 6 months and 12 months.
Results	For TTSTAND velocity: The results numerically favoured vamorolone 6 mg/kg/day over prednisone at six months (LSM difference: 0.0023 rises/second [95% CI: -0.0297 to 0.0344). In contrast, at 12 months, results numerically favoured prednisone (LSM difference: -0.0016 rises/second [95% CI: -0.0365 to

	0.0333]). However, 95% CIs crossed 0, suggesting no evidence of a difference between treatment groups. At both the 6 months (LSM difference -0.0044 rises/second [95% CI: -0.0326 to 0.0238]) and 12 months timepoints (LSM difference -0.0015 rises/second [95% CI: -0.0324 to 0.0293]), the results numerically favoured deflazacort over vamorolone 6 mg/kg/day. However, 95% CIs crossed 0, suggesting no evidence of a difference between treatment groups. With regards to the other efficacy outcomes: 6MWT; TTRW and NSAA score; the results of the comparisons were broadly similar across treatments at 6 and 12 months. The European regulator concluded that there were no clinically meaningful differences between the studies for any of the efficacy outcomes. Patients that received vamorolone had an absence of growth stunting compared to patients that received prednisolone or deflazacort. Weight results were deemed not valid by the submitting company. Adverse events were similar across treatment groups.

Abbreviations: 6MWT = 6-minute walk test; CI = confidence interval; DMD = Duchenne muscular dystrophy; LSM = least squares mean; mITT = modified intent-to-treat; NSAA = North Star Ambulatory Assessment; NSS = not statistically significant; SD = standard deviation; SE = standard error; TTRW = time to run or walk 10 metres; TTSTAND = time to stand from supine.

3. Summary of Safety Evidence

Overall, no new safety issues have been identified with vamorolone treatment as compared to conventional glucocorticoids.[2,13] Only vamorolone 6mg/kg/day is discussed hereafter in the safety section, as this is the licensed starting dose for patients < 40kg.[1]

In VISION-DMD at Week 24, any treatment-emergent adverse event (AE) was reported by 89% in the vamorolone 6 mg/kg/day group, 84% in the prednisone group, and 79% in the placebo group; these were considered treatment-related in 68%, 45%, and 28%, respectively. The vast majority of treatment-emergent AEs were either mild or moderate. Three serious AEs were reported in VISION-DMD (up to week 48), none of which were considered treatment-related.[2, 9, 11]

The following are AEs of special interest (AESIs) that have been inputted into the economic case; at week 24 in the vamorolone 6 mg/kg/day (VISION-DMD), prednisone (VISION-DMD), and placebo groups (VISION-DMD) respectively are: weight gain (18%, 9.7%, 6.9%); behaviour problems (21%, 32%, 14%); cushingoid features (29%, 23%, 0%); infections (32%, 39%, 45%); gastrointestinal symptoms (29%, 26%, 28%) diabetic conditions (3.6%, 9.7%, 3.4%); and skin/hair changes (3.6%, 13%, 6.9%).[2, 9, 12]

One of the quantitative differences in the safety profile that appears to be in favour of vamorolone compared with prednisone was the absence of a growth stunting effect for vamorolone. Additionally, available data suggests that vamorolone does not, or at least to a lesser extent than prednisone, adversely affect bone health.[2, 9, 11]

Aspects of the safety profile for vamorolone 6 mg/kg/day that are similar to or worse than prednisone in the controlled setting include: more pronounced adrenal suppression (mean change in morning cortisol from baseline was -7.06 versus -5.17 micrograms/dL), more cushingoid features (29% versus 23%); unwanted weight gain and BMI increases (18% versus 9.7%); and increased fasting insulin levels (27% versus 18%).[2]

For those treated with vamorolone, behaviour problems were reported in the first 6 months of treatment, with the majority of behaviour problems occurring in the first 3 months of treatment and resolving without treatment discontinuation. Behaviour problems were reported at a higher frequency in the prednisone group (32%) compared to the vamorolone 6 mg/kg/day group (21%); though mild irritability was more frequently reported in the vamorolone 6 mg/kg/day group (10.7% versus 3.2%).[2]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Data to support the efficacy of vamorolone is available from VISION-DMD, a randomised, double-blind, phase IIb study that included a treatment arm with a relevant active comparator (prednisone).[2, 3]
- In VISION-DMD, clinically meaningful benefits were observed in outcomes relevant to DMD for both doses of vamorolone compared with placebo[2, 9]
- The study was not powered to detect differences between vamorolone and prednisone. However, the improvements seen with vamorolone 6 mg/kg/day in the TTSTAND, TTRW, and TTCLIMB velocity outcomes were similar to those seen with prednisone at Week 24.[2]
- Limited long-term data of up to 30 months of treatment suggests results for vamorolone are maintained.[2, 10, 12]
- Some patients with DMD are unable to take corticosteroids due to adverse events. Vamorolone may have a reduced incidence of some specific adverse effects such as stunted growth and bone health compared with corticosteroids.[2, 9, 11]

4.2. Key uncertainties

- VISION-DMD recruited patients aged 4 to >7 years of age therefore there is uncertainty about the effect of vamorolone in older patients and those in later stages of the condition.[2] The submitting company highlighted some safety data from the ongoing VBP-006 study (open-label, multiple-dose, phase II), where 16 patients aged >7 to 18 years old who had prior corticosteroid use (mean duration of treatment of 53.6 months) were switched to 6.0 mg/kg/day[13] which indicates that vamorolone is safe and tolerable in patients > 7 years of age. However, there is still an absence of efficacy results from VBP15-006 (due in November 2024).
- As per the licensed indication, vamorolone may also be administered as a subsequent treatment option after corticosteroids[1]. However, patients in VISION-DMD were naïve to corticosteroids at baseline, meaning it is uncertain what effect prior corticosteroids will have on the efficacy of vamorolone.[2] Patients in the prednisone group that switched to vamorolone 6 mg/kg/day after 24 weeks did not experience a loss of efficacy[2], however, this only provides evidence (from an open-label extension phase) for those who have had only 6 months of prior

corticosteroid exposure. It is likely that at least some DMD patients in clinical practice will have already received corticosteroids (and for more than 6 months).

- In VISION-DMD only the first 6 months were controlled, this makes the week 24 to 48 data difficult to interpret. Evidence about the long-term effects of treatment is lacking.[2, 12] Additionally, there are a lack of data regarding the effects on fracture risk and pubertal delay, which experts have highlighted as important to patients with DMD.[2]
- Overall, the submitting company's conclusion of equivalent (equal) efficacy between vamorolone 6 mg/kg/day and prednisone is uncertain. The study design of VISION-DMD tested the superiority of both vamorolone doses over placebo but no formal statistical testing was carried out between any vamorolone dosing group and prednisone. Improvements observed with vamorolone were numerically similar to prednisone for some outcomes, however prednisone was numerically better for others.[2]
- Prednisolone and deflazacort are the most relevant comparators. Prednisolone is generally accepted to be equivalent to prednisone (the comparator used in the key study), however direct data versus deflazacort are not available. An indirect treatment comparison (ITC) of both vamorolone dose groups to prednisone and deflazacort from a matched external control was presented. The ITC had limitations including methodological differences and the inclusion of small patient numbers. For methodological reasons, equivalent (equal) efficacy could not be concluded from the ITC, though the conclusion of comparable efficacy between vamorolone 6 mg/kg/day and prednisone/deflazacort appears reasonable.[2]
- In the case of tolerability issues, there is an option for dose reduction from 6 mg/kg/day to 4 mg/kg/day (not assessed in this submission) or 2 mg/kg/day.[1] However, inconsistent results from the direct evidence (weeks 24 to 48) mean that the maintenance of efficacy seen at week 24 could not be demonstrated for the 2 mg/kg/day dose. Additionally, the indirect evidence results suggest that vamorolone 2 mg/kg/day is inferior in efficacy to both prednisone and deflazacort.[2]
- Some significant adverse effects occurred more frequently in patients receiving vamorolone than prednisone such as more pronounced adrenal suppression and cushingoid features; unwanted weight gain and BMI increases; and increased fasting insulin levels.[2]

4.3. Clinical expert input

Clinical experts consulted by SMC advised that vamorolone is a therapeutic advance due to potential benefits on growth and bone health compared with corticosteroids. They considered that it would fill an unmet need for these patients, namely as an alternative to corticosteroids.

4.4. Service implications

Some clinical experts consulted by SMC advised that there could potentially be a significant initial administrative workload for commencing patients on vamorolone who are on no treatment or who are switching from corticosteroids. However, the ongoing management for these patients would then be expected to be very similar to current DMD patient management.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of **vamorolone (Agamree®),** as an **orphan** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Duchenne muscular dystrophy (DMD) is a rare, severe, life-limiting, X-linked recessive genetic condition that causes muscle weakness leading to progressive disability. DMD has a poor prognosis, with a life expectancy of approximately 30 years. There is a significant mental and emotional burden attached with the diagnosis of DMD and since this is a genetic condition, the diagnosis can have an even greater devastating impact on larger families who may have multiple children with DMD.
- Children with DMD experience a decline in muscle strength from as young as 2 years old. Gradually over the first 2 decades of life, DMD leads to them being unable to run, climb stairs, and eventually unable to walk and stand; meaning they have a dependency on wheelchair support from an early age. Eventually people with DMD also lose their arm mobility and strength and by the age of 18, most patients require ventilatory support. This condition slowly robs patients of their independence as they require assistance with all self-care activities like eating, drinking, toileting, dressing, washing, and being moved into and out of bed.
- The condition also causes other significant systemic complications such as scoliosis, joint contractures, respiratory and cardiac failure, and arrhythmias. As well as the physical complications, there are also significant impacts on social communication, learning and concentration. Overall, DMD has a devastating effect on families and severely limits the young people who are affected.
- There is no cure for DMD and whilst chronic corticosteroid treatment (specifically prednisolone and deflazacort) has been shown to temporarily reduce the motor function decline, they are associated with significant side effects which can significantly reduce the quality of life of these young people and their families/carers; so much so that some opt for no treatment in preference for steroid-induced side effects. Therefore, there remains a significant unmet need for an alternative efficacious treatment that is better tolerated.
- PACE participants highlighted the positive responses from patients with DMD who have received vamorolone participating in a clinical trial.
- However, PACE participants highlighted that the main advantage of vamorolone over corticosteroids is its alternative side effect profile. They recognised that vamorolone is not the “perfect medicine”, but they all agreed that vamorolone would still provide significant benefits based on its side effect profile; some patients may even be prepared to accept reduced ambulation time with vamorolone (compared with corticosteroids) to avoid the issues of stunted growth and fracture risk. However, it is also important to recognise that ambulation is a proxy measure of overall disease progression.
- PACE participants highlighted the negative effects corticosteroids have on physical appearance

such as significantly stunted height, which can result in them being stigmatised and ostracised by their peers resulting in low self-esteem and poor mental health. The absence of this side effect would have an enormous positive impact to their quality of life.

- PACE participants highlighted published data that has been presented in scientific conferences which suggests that vamorolone has a lower risk of vertebral fractures compared with regular corticosteroid use. Given the association between these fractures and premature loss of ambulation in patients with DMD, this would translate into a significantly positive improvement in quality of life and could mean less hospital admissions for fracture treatment and prevention (for example with bisphosphonate infusions).
- Vamorolone may also have fewer negative effects on behaviour than corticosteroids, however further data is needed to confirm this association between vamorolone and behavioural issues.
- Vamorolone comes as an oral suspension, in contrast to prednisolone and deflazacort, which come as soluble tablets; meaning vamorolone would be much easier for parents/carers to administer to their child.
- The introduction of vamorolone could potentially be of significant administrative workload for corticosteroid naïve patients or transitioning those who are already on corticosteroids. However, the ongoing management for these patients would then be expected to be very similar to current DMD patient management.

Additional Patient and Carer Involvement

We received a joint patient group submission from: Action Duchenne, Duchenne UK and Muscular Dystrophy UK. All three organisations are registered charities. Action Duchenne has received 36.7% pharmaceutical company funding in the past two years, including from the submitting company. Duchenne UK has received 11.32% pharmaceutical company funding in the past two years, including from the submitting company. Muscular Dystrophy UK has received 1.32% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from the three patient groups participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case is presented in table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	95 years.
Population	The economic patient population considered was glucocorticoid-naïve boys aged four years and above with DMD. However, the licensed indication is for a wider population group as it is not restricted to glucocorticoid-naïve patients. The company assumed the results will be generalisable to treatment experienced patients.

Comparators	Prednisone and deflazacort were deemed the most relevant comparators by the submitting company. Prednisolone is used in practice, but is considered clinically equivalent to prednisone. The model accounted for this by using prednisolone prices for the prednisone comparator.
Model description	A Markov model utilising the natural history model "Project HERCULES".[14, 15] The model comprised of ambulatory and non-ambulatory health states, plus an intermediate 'Transfer' health state, and death state. Cycle length is 1 month, with a half-cycle correction applied. No backward progression was permitted, and patients may only progress to adjacent states.
Clinical data	Clinical data were taken from the VISION-DMD study.[9, 11] Long-term efficacy outcomes for vamorolone were obtained from a combination of the UK NPP and VBP15-LTE study.[10] As many patients are unable to tolerate full dose of corticosteroids in a real-world setting, long-term efficacy of down-titrated prednisone and deflazacort were obtained from FOR-DMD[12] and the CINRG[16] data set. The submitting company presented a patient level matched comparison because there was a lack of both long-term efficacy data, as well as direct evidence of vamorolone compared with prednisolone or deflazacort (see section 2.4 above). The two studies used were: VISION-DMD and FOR-DMD. The company concluded that vamorolone and prednisone were equivalent when considering muscle function outcomes. It also assumed that deflazacort was equivalent to prednisone for the indirect comparison. Adverse event incidence rates were sourced from VISION-DMD for vamorolone and prednisone patients, and FOR-DMD was used for deflazacort adverse event incidence rates.
Extrapolation	The natural history transition (NHM) probabilities used to extrapolate efficacy beyond the study data were taken from Project HERCULES.[14, 15] The NHM assumed a constant progression rate in each state which was split into patients below and over 30 years old. Given the comparable efficacy assumption, all treatments result in the same transition probabilities taken from Project HERCULES. The model allowed for patients to down-titrate the dose of their respective treatments, where it was assumed that vamorolone patients would not experience any reduction in efficacy, but prednisone and deflazacort would experience a reduction in efficacy. This is a key driver of the estimated improved outcomes with vamorolone in the model. Patients could discontinue treatment, where a uniform discontinuation rate was applied across treatment arms. This discontinuation rate was sourced from Kaplan-Meier analysis of deflazacort from CINRG data, using a log-normal curve.[16] If patients did not discontinue, it was assumed treatment duration would be until death. Due to the short follow up of the VISION-DMD study, mortality and survival probabilities were sourced from Broomfield et al., 2021[14], and then extrapolated using the generalised gamma curve.
Quality of life	EQ-5D data were not available from the VISION-DMD study. Patient utilities were taken from Landfeldt (2023)[17] in the base case, with the Landfeldt et al., (2017)[18] study used in scenario analysis. Utility decrements were applied to all acute events, adverse events of special interest and comorbidities. Both moderate/severe and mild adverse events were included. A proxy approach was used for mild adverse event disutilities by applying 25% of the disutility for moderate/severe adverse events. Carer utilities were included in a scenario analysis where the utility values were taken from Landfeldt et al.,(2017)[18] and an additional disutility decrement was applied to carers when patients experience behavioural issues. Joseph et al., 2019[6], was used to inform adverse events such as fracture data within the model.
Costs and resource use	Costs included medicine acquisition, health state costs, adverse events and comorbidity costs. All treatments are self-administered so no administration costs were included in the model. 10mg soluble prednisolone BNF prices were used for the prednisone arm, however in clinical practice the 5mg (x2)

	prednisolone tablets would more likely be used. No subsequent treatments costs were included, due to the design of clinical studies and therefore no treatment sequencing was modelled.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. A discount was offered on the list price.

6.2. Results

Table 6.2 illustrates the base case results comparing vamorolone to prednisone and deflazacort.

Table 6.2a: Base case results with PAS

Technologies	ICER (£/QALY)
vamorolone vs prednisone	£15,247
vamorolone vs deflazacort	£10,648

Abbreviations: ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALY = quality-adjusted life year.

To summarise, the main cost driver was the differences in medicine costs with vamorolone costing substantially more than the comparators. This was slightly offset by the differences in costs for full-time ventilation between the treatments. This was directly linked to the asymmetric assumptions around down-titration efficacy between treatment arms, since the comparator arm was losing efficacy after down-titration, therefore more of the comparator patients progressed to the more severe health states faster.

The driver in quality-adjusted life-years (QALYs) can be seen in an increase in QALYs gained in the early ambulatory health state for vamorolone and the large loss in QALYs due to adverse events for the comparators. The increase in QALYs in the early ambulatory health state was again linked to the assumptions around down-titration between treatment arms, where the vamorolone arm was assumed to not have any reduction in efficacy. Therefore, vamorolone accrued QALYs in this health state over a longer duration. The QALY loss for adverse events in the comparator arms is due to the assumption that vamorolone displayed a better safety profile (for example behavioural issues, cataracts, stunted growth).

6.3. Sensitivity analyses

A deterministic, probabilistic and scenario analysis was performed. Deterministic sensitivity analyses highlighted that the key parameters that influenced the incremental cost-effectiveness ratio (ICER) were behavioural issues (incidence, duration, and disutility inputs), the transition hazard ratios for each treatment, the full-time ventilation costs and the efficacy of down-titration of each treatment arm.

Selected scenarios from the scenario analysis are displayed in table 6.3.

Table 6.3: Selected scenarios explored in the cost-effectiveness analysis with PAS

	Parameter	Base case	Scenario	ICER (£/QALY) vs prednisone	ICER (£/QALY) vs deflazacort
	Base case			£15,247	£10,648
1	Caregiver QALYs	Excluded	Included	£6,743	£5,174
2	Time horizon	95 years	50 years	£15,070	£10,919
3	Efficacy of vamorolone	Vamorolone, prednisone and deflazacort have the same transition probabilities	5% reduction in efficacy for vamorolone only	£16,324	£11,543
4			10% reduction in efficacy for vamorolone only	£17,488	£12,507
5	Vamorolone down-titrated efficacy	No reduction in efficacy when vamorolone is down-titrated to 4m/kg/day	Reduced efficacy - HR 1.075 is applied to the transition probabilities	£15,741	£11,021
6	CS down-titrated efficacy	Reduction in efficacy	No reduction in efficacy	£30,143	£21,168
7	Reduced AEs from down-titrating	Individual reduction for AEs resulting in an average 18% reduction	No reduction in AEs from down-titrating	£12,733	£8,835
8	Stunted growth duration	8 years	20 years (lifetime)	£13,278	£8,242
9	Behavioural issues duration	4.5 years	1.5 years	£27,901	£18,310
10	Health state utilities (patient)	Landfeldt 2023	Landfeldt et al. 2017	£14,064	£9,948
11	Adverse event incidence rates for vamorolone arm	Incidence rates sourced from VISION-DMD study	Vamorolone behavioural issues, cataracts and stunted growth increased to 30% of comparator rates	£17,457	£12,881
12	Combined scenario	- Comparable efficacy - Reduction in efficacy for CS when down-titrated - Behavioural issues, cataracts and stunted growth for vamorolone in line with VISION-DMD	- 10% reduction in efficacy of vamorolone, - No reduction in efficacy when CS down-titrated - Increased AE rates with vamorolone	£38,623	£28,592

	Parameter	Base case	Scenario	ICER (£/QALY) vs prednisone	ICER (£/QALY) vs deflazacort
13	Combined scenario	- No reduction in efficacy for vamorolone - Reduction in efficacy for the comparators when down-titrated - Behavioural issues, cataracts and stunted growth for vamorolone in line with VISION-DMD - Carer QALYs excluded	- 10% reduction in efficacy of vamorolone, - No reduction in efficacy when CS down-titrated, - Increased AEs rates with vamorolone - Carer QALYs included	£17,540	£14,437
14	Discontinuation rate for prednisone	CINRG deflazacort discontinuation data for all treatment arms	CINRG prednisone discontinuation data used for the prednisone arm	£12,681	£10,648
15	Stopping rule	No stopping rule	Treatments are stopped at loss of ambulation	Dominant (-£4,940)	Dominant (-£8,795)
16	Efficacy of vamorolone when down-titrated	No reduction in efficacy when down-titrated	Reduction in efficacy when down-titrated	£15,863	£11,107
17	Combined scenario	- No reduction in efficacy when down-titrated - All treatments have comparable efficacy at full dose	- Reduction in efficacy when down-titrated - 5% reduction in vamorolone efficacy at full dose	£16,932	£11,989
18	Combined scenario	- Stunted growth set at 8 years - Behavioural issues set at 4.5 years - Incidence rates of behavioural issues, cataracts, and stunted growth in line with VISION-DMD	- Stunted growth set at 20 years - Behavioural issues reduced to 1.5 years - Increased AE rates for vamorolone	£25,910	£15,181
19	Combined scenario	- No reduction in efficacy for vamorolone - Reduction in efficacy for CS	- 10% reduction in efficacy of vamorolone, - No reduction in efficacy when	£54,761	£38,545

	Parameter	Base case	Scenario	ICER (£/QALY) vs prednisone	ICER (£/QALY) vs deflazacort
		when down-titrated - Behavioural issues, cataracts and stunted growth for vamorolone in line with VISION-DMD - Behavioural issue duration set to 4.5 years	CS are down-titrated - Increased AE rates with vamorolone - Reduction in behavioural issues duration to 3 years		
20	Combined scenario	- No reduction in efficacy for vamorolone - No reduction in vamorolone efficacy when down-titrated - Behavioural issues, cataracts and stunted growth for vamorolone in line with VISION-DMD - Behavioural issue duration set to 4.5 years	- 10% reduction in efficacy of full dose vamorolone, - Reduction in vamorolone efficacy when down-titrated - Increased AE rates with vamorolone - Reduction in behavioural issues duration to 3 years	£27,242	£20,012

Abbreviations: AE = adverse events; CS = corticosteroids; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; QALYs = quality-adjusted life years; QoL = quality of life.

6.4. Key strengths

- The model structure was reasonable, and the health states were appropriate.
- Transition probabilities sourced from Project HERCULES' Natural History Model, for the full doses of the treatments, seemed reasonable and appropriate.
- While prednisolone would be the most relevant comparator in Scottish clinical practice, as prednisone and prednisolone are deemed clinically equivalent, the comparators are appropriate.

6.5. Key uncertainties

- The economic model focused exclusively on corticosteroid naïve patients with the implicit assumption that results would generalise to the broader population covered by the licence. The model does not allow for potential differences in outcomes for those previously treated with corticosteroids and does not account for subsequent treatment options or treatment switching. It is unclear whether the results would be generalisable to all patients within the licensed indication.
- The economic model assumed comparable efficacy between vamorolone, prednisone and

deflazacort, with the same transition probabilities applied in the project HERCULES natural history model for each treatment at full dose. However, this assumption is uncertain. The study design of VISION-DMD tested the superiority of both vamorolone doses over placebo but no formal statistical testing was carried out between any vamorolone dosing group and prednisone. Additionally, there was a lack of direct evidence against deflazacort and lack of long-term efficacy data available against all comparators. However, scenarios 3 and 4 in table 6.3 demonstrate only modest increases in the ICER when the efficacy of vamorolone is reduced by 5% or 10% compared to the comparators.

- The submitting company assumed no change in efficacy when vamorolone is down-titrated from 6mg/kg/day to 4mg/kg/day, while applying a reduction in efficacy in the comparator arms when down-titrated. This approach allowed vamorolone to have a sustained treatment effect at a reduced cost. However, this assumption was not supported by direct evidence, as the 4mg/kg/day dose was not used in the VISION-DMD study. The available evidence from VISION-DMD demonstrated a reduction in efficacy when vamorolone was down-titrated from 6mg/kg/day to 2mg/kg/day, raising concerns about the validity of the modelled assumption. For the comparators, the application of a hazard ratio to account for reduced efficacy resulted in faster progression through the model, leading to increased costs and greater time spent in more severe health states. When the efficacy reduction for prednisone and deflazacort was removed (scenario 6), a substantial increase in the ICER was observed.
- The submitting company reported a reduced incidence rate for moderate/severe behavioural issues, and no incidences of stunted growth and cataracts among patients who received vamorolone. This was based on evidence from the 24-week VISION-DMD study. Scenario 11 in table 6.3 shows an increase in the ICER when the incidence rates for behavioural issues, stunted growth and cataracts in the vamorolone arm are increased. Given the limited duration of VISION-DMD, there is uncertainty surrounding the validity of these assumptions.
- The model used a uniform discontinuation rate across all treatments, sourced from a KM analysis of deflazacort using CINRG data. The company opted to not use the CINRG prednisone curve for the prednisone arm due to their clinical experts suggesting that the extrapolated CINRG discontinuation rate for prednisone was too high. This creates some uncertainty as scenario 14 in table 6.3 illustrates an increase in the ICER when the prednisone CINRG discontinuation curve was used for the prednisone arm.

7. Conclusion

The Committee considered the benefits of vamorolone in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as vamorolone is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted vamorolone for use in NHSScotland.

8. Guidelines and Protocols

In 2018, the international DMD care considerations working group published the following guideline: Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management.[3]

The Scottish Muscle Network is the nationally managed clinical network for children and adults with neuromuscular disorders, including DMD. These include the Scottish Muscle Network Duchenne Muscular Dystrophy (DMD) Scottish Physiotherapy management profile which provides useful information about steroid therapy.[4]

9. Additional Information

9.1. Product availability date

15 December 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Vamorolone 40 mg/mL oral suspension	**Administered orally:** • **If < 40 kg: 6 mg/kg once daily.** • **If > 40 kg: 240 mg once daily.**	**If > 40 kg and assuming no down-titration:** £100,155 **If < 40 kg and assuming no down-titration:** £32,101 to £98,653 (ranging from 12 kg to 39 kg) The UK list price (excluding VAT) for 100ml of 40mg/ml of vamorolone is £4,585.87.

Costs from the company submission on 28 August 2024. Costs do not take any patient access schemes into consideration. Mean body weight at baseline was 19.6 kg in VISION-DMD, the lowest weight percentile (0.4th) for a 4-year old according to UK-WHO chart for boys is approximately 12 kg.[19]

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 77 patients eligible for treatment with vamorolone in year 1 rising to 93 in year 5. The estimated uptake rate was 14 % in year 1 and 46% in year 5 with a discontinuation rate of 0.6 % in year 1 rising to 1.2 % in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 27 November 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the

operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.