NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Call for additional evidence

Givinostat for treating Duchenne muscular dystrophy in people 6 years and over

Committee discussion and call for additional evidence

The evaluation committee discussed this appraisal at its committee meeting in July 2025. It considered evidence submitted by ITF Pharma UK, a review of this submission by the external assessment group (EAG), and responses from stakeholders, including evidence submitted during the technical engagement. It also heard evidence and testimony raised by experts during the meeting. See the committee papers for full details of the evidence.

In its extensive discussion and deliberations, the committee took into account the nature of this rare, serious, progressive, fatal condition that begins in childhood, alongside the available evidence on clinical and cost effectiveness of givinostat. The committee was unable to reach a full conclusion, because it considered that more evidence is needed before it could make a fully informed decision. Therefore, the committee outlined additional information and analyses that it would need to determine whether givinostat should be recommended as an option in the NHS.

Stakeholder organisations and invited experts who are participating in the appraisal are invited to submit additional evidence to support the committee's decision making, as outlined in this document. You are encouraged to focus on the issues highlighted in the following sections. NICE will also consider any other points raised as appropriate. NICE is not able to accept comments from individuals, including people with Duchenne muscular dystrophy, family members or clinicians, unless they are

Issue date: August 2025

the invited experts. People are encouraged to contact participating organisations. Submission details and instructions are provided separately.

Duchenne muscular dystrophy

Duchenne muscular dystrophy is a rare, severe, and progressive genetic condition caused by mutations in the dystrophin gene, which is essential for maintaining muscle fibre integrity. Without dystrophin, muscles gradually weaken and degenerate. Because the gene is located on the X chromosome, the condition primarily affects boys and men, although in rare cases, girls may also be affected.

In the UK, around 100 people are born with Duchenne muscular dystrophy each year, and approximately 1,183 are currently living with the condition. Symptoms typically begin between ages 2 and 5, including delayed motor milestones, frequent falls, enlarged calf muscles, and Gower's sign. As the condition progresses, individuals lose the ability to walk, followed by loss of upper limb function, respiratory decline, and heart complications such as cardiomyopathy.

Most people with Duchenne muscular dystrophy require full-time support for daily activities including eating, dressing, and moving. Mobility aids such as wheelchairs become essential, and regular monitoring of the spine, heart, and breathing is needed. Scoliosis may develop and require surgery. Most people need ventilatory support in their teens or early twenties, including overnight non-invasive ventilation (a method of supporting breathing using a mask or mouthpiece, which helps maintain oxygen levels and reduce strain on weakened respiratory muscles) and cough assistance.

As dependence increases, families and carers play a central role in daily care. Duchenne muscular dystrophy is a fatal condition, and life expectancy is typically under 30 years.

Impact of the condition

Duchenne muscular dystrophy has a profound and wide-ranging impact on the lives of people with the condition and their families. The progressive loss of muscle

function, and associated loss of mobility and independence, leads to significant emotional, psychological, and physical strain. Support from carers is needed from the early stages of the disease. As the condition advances, full-time care is required. This has a substantial and sustained effect on carers. Siblings may also be affected emotionally, experiencing worry, guilt, or isolation, and their lives are often shaped by the needs and routines of the family member with Duchenne muscular dystrophy.

The patient and clinical experts highlighted that there is an unmet need for treatments that can slow disease progression. Maintaining the ability to move independently and using arms and hands for as long as possible is seen as essential for preserving independence, mental wellbeing, and participation in everyday life. One particularly important stage is known as the transfer stage, when a person can no longer walk but can still stand with support. A patient expert described how her 19-year-old son, who is still in the transfer stage, remains highly independent. He can work, travel, and with support, move independently. This level of independence has a profound impact on his quality of life and reduces the impact on carers.

The committee heard about the importance of delaying the loss of mobility and maintaining independence particularly during the teenage years. This is a time when most young people are gaining greater freedom, learning to drive, attending university, and spending more time with friends. While young people with Duchenne muscular dystrophy may be experiencing the opposite, increasing dependence. This contrast can be emotionally challenging and isolating. For some people with the condition, the loss of mobility can also be associated with experiences of bullying or social exclusion, further affecting mental health and self-esteem.

Delaying the loss of mobility can help preserve a sense of autonomy and self-worth and may allow young people to continue doing things that are important to them, such as attending university lectures, participating in social life and pursuing their interests. These aspects of independence are not only practical but are also deeply connected to emotional wellbeing, identity, and inclusion. Being able to maintain independence for longer can help people with Duchenne muscular dystrophy continue to engage in education, relationships, and other key parts of growing up.

The committee understood that Duchenne muscular dystrophy is a severe, progressive, and life-limiting condition that imposes a substantial and enduring impact on individuals, their families, and carers, affecting physical health, emotional wellbeing, and quality of life.

Company's positioning of givinostat

The company restricted the population in its submission to people 6 years and over who are ambulant at the start of treatment. This is consistent with the population in the EPIDYS trial and the open-label extension (OLE) study.

But givinostat is licensed for the treatment of Duchenne muscular dystrophy in people 6 years and over, regardless of whether they are ambulant at the start of treatment. The clinical experts noted that people who are non-ambulant may still benefit from treatment, and that restricting access based on ambulation status could exclude people who might otherwise experience important improvements. The patient experts thought that givinostat should be available to all people with Duchenne muscular dystrophy and that it would be unfair to deny this treatment to people who had already lost ambulation.

The company explained that at the time of submission, it only had evidence for the ambulant starting population so it could therefore only model the cost effectiveness of givinostat in this population. It noted that a trial, ULYSSES, was underway to assess givinostat in a non-ambulant starting population.

The committee acknowledged the broader licensed population and the views of clinical and patient experts. But it concluded that, while the appraisal scope includes the full marketing authorisation population, it could only consider this full population if sufficient evidence was submitted. On balance, the committee agreed that it was not possible to make recommendations beyond the narrower population for which the company had submitted evidence. So, the committee could only consider the ambulant starting population in its decision making.

Committee call for additional evidence

The committee recognised the high unmet need for effective treatments for Duchenne muscular dystrophy but because of high level of uncertainty in the evidence it was not able make a fully informed decision. The areas with most uncertainty were:

1. the estimation of givinostat treatment effect and its application in the model
2. the carer health-related quality-of-life modelling and assumptions
3. the patient health-related quality-of-life modelling and assumptions
4. the resource cost modelling and assumptions.

Therefore, the committee outlined the additional information and analyses that it would need to inform decision making.

Estimation of givinostat treatment effect and application in the model

- Explore alternatives to the company's acceleration factor-based approach (for example, applying the hazard ratios from the unanchored matching-adjusted indirect comparisons [MAIC] directly to the transitions); further justification that the relationship between outcomes would be the same between givinostat and established clinical management (ECM).
- Clarify whether the company's current approach modelled a treatment effect beyond loss of ambulation; clear explanation distinguishing between direct effects of ongoing givinostat treatment in non-ambulant patients and indirect (or knock-on) effects resulting from delaying disease progression during the ambulatory phase.
- If modelled, justify the magnitude of any post loss-of-ambulation treatment effect, and explore how uncertainty in longer-term treatment effects could otherwise be incorporated into decision making.
- Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling the givinostat treatment effect.

Carer health-related quality-of-life modelling and assumptions

The committee acknowledged the sensitivity and critical importance of this issue for patients and families, and the substantial technical challenges associated with it. It also highlighted the substantial effect it had on the cost-effectiveness of givinostat. The committee recognised that it was important to ensure carer health-related quality of life was appropriately and robustly considered in decision making. The committee considered that it was not appropriate to assume that extending the life of someone with Duchenne muscular dystrophy would have no direct effect on carers' health-related quality of life. But, it also acknowledged that extending time in health states associated with a negative impact on carers' would extend that negative impact. The committee also highlighted important limitations and uncertainties in both the company's and EAG's approaches, including the number of carers, utility values and methodological approach.

The committee concluded that carer health-related quality of life needed to be captured appropriately, but neither the company's nor the EAG's approaches to quantify this had done so. It therefore concluded that further information and modelling was needed.

- Present updated economic modelling based on plausible, evidence-based and fully justified approaches to modelling effects on carer health-related quality of life, considering in particular:

  Approach to modelling (increments from midway, disutilities):
  - Comment on the rationale, implications and plausibility of each method, including the justification for using increments or disutilities compared to selected health states or general population values.
  - Ensure that the approach captures the increasing impact on carers as the condition progresses.
  - Explain why in the current model, the approaches produce different results if the numbers of carers are not equal in all health states (including in scenarios that do not model carers in state 9).

Utility source

- Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et al. (2016a), and comment on the consistency in utility modelling between patient and carer utilities.
- Present analyses based on all sources of carer utilities.
- Explore different ways to differentiate between health states 7 and 8 for all possible sources.

Number of carers in ambulatory health states:

- Explore scenarios modelling between 1 and 2 carers in ambulatory states to better reflect the overall magnitude of effects on carer health-related quality of life (with 2 carers in the non-ambulatory health states).

Life-extension effect on carer health-related quality of life

- The committee was aware that modelling relating to the effects of life extension on carer health-related quality of life has a large impact on the ICER. The committee considered that it was unreasonable for the model to assume that there would be no negative effect of losing a child on health-related quality of life. But, it also considered that the company's approach and increment of -0.56 (implying a carer utility of 0) was not evidence based and may not be appropriate. It further acknowledged that extending time in health states with a negative effect on carers would extend that negative effect during that period.
- Therefore, explore and justify different approaches for modelling the effect of life extension on carers. This may include using different utilities for health state 9, and must take into account strengths and limitations of different methodological approaches for modelling life-extension effect on carer health-related quality of life.

Patient health-related quality-of-life modelling and assumptions

- Clarify and justify how reported utility values were assigned to model health states. Justify the appropriateness of Landfeldt et al. (2017) versus Landfeldt et

al. (2016b), and comment on the consistency in utility modelling between patient and carer utilities.
- Explore patient health-related quality of life informed by Crossnohere et al. (2021).
- Capture the increasing impact on patients as the condition progresses; explore different ways to differentiate between health states 7 and 8 for all possible sources (for example, by combining models 2 and 3 from Landfeldt et al. 2017).

Resource cost modelling and assumptions

- Further explore tertiary-care and medical-aid costs.
- Ensure scenarios differentiate between health states 7 and 8.

Equality

- Describe any further issues of equality that the committee should take into account in its decision making.

Committee other considerations

The committee reached conclusions on some issues and preferred assumptions. It requested that analyses be presented using these conclusions and preferred assumptions. Specifically:

- use ECM based on treatment regimens used in EPIDYS as a comparator
- use the UK real-world dataset as a source for ECM data in the unanchored MAIC
- use the full givinostat population from EPIDYS and the OLE study (n=224) as a source of givinostat data for the unanchored MAIC
- use the reference-case discount rate of 3.5% for costs and health effects, throughout the model time horizon
- use the company's updated natural history model.