NCPE Technical Summary

Givinostat (Duvyzat®)

HTA ID: 25048

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Applicant: ITF Pharma UK & Ireland

The cost-effectiveness of givinostat for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients aged six years and older with concomitant corticosteroid treatment.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of givinostat (Duvyzat®) for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients aged six years and older with concomitant corticosteroid treatment. Following assessment of the Applicant's submission, the NCPE recommends that givinostat (Duvyzat®) not be considered for reimbursement for this indication unless cost-effectiveness can be improved.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (ITF Pharma UK & Ireland) Health Technology Assessment (HTA) of givinostat (Duvyzat®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In January 2026, ITF Pharma UK & Ireland submitted a dossier which investigated the clinical effectiveness, cost-effectiveness and budget impact of givinostat for the treatment of Duchenne muscular dystrophy (DMD) in ambulant patients aged six years and older with concomitant corticosteroid treatment. Reimbursement is sought under the High Tech Drug Arrangement.

Duchenne muscular dystrophy (DMD) is a severe X-linked recessive disorder caused by mutations in the dystrophin gene and consequent complete loss of dystrophin protein expression. Although asymptomatic at birth, gradual muscle weakness and wasting are first apparent in proximal limb muscles before spreading to more distal muscles leading to the diagnosis in the first few years of life. Early symptoms, between ages two and three years include a waddling gait, frequent falls, difficulty in standing from a seated position and difficulties in climbing stairs. Affected children exhibit delayed gross motor development and at ages 10 to 12 years many patients require the use of a wheelchair. As muscle weakness progresses, scoliosis and joint contractures develop, which may be associated with restrictive lung disease. An increased risk of pneumonia and atelectasis in addition to compromised diaphragmatic function can cause severe respiratory insufficiency. Life-threatening consequences of cardiac muscle dystrophin deficiency include dilated cardiomyopathy, cardiac arrhythmias and heart failure. Assisted ventilation may be necessary by 15 to 20 years of age and many DMD patients die from cardiac and/or respiratory failure between 20 and 30 years of age despite optimal care.

Whilst systemic corticosteroids are the mainstay of treatment for DMD and they delay loss of muscle strength and function, the undesirable adverse effects often require dose reductions. The optimal dose and regimen of corticosteroids are unclear although daily prednisone appears preferable to intermittent prednisone.

Givinostat (Duvyzat®) is indicated for the treatment of DMD in ambulant patients, aged six years and older, with concomitant corticosteroid treatment. It obtained conditional marketing authorisation from the European Medicines Agency (EMA) on the 6th of June 2025. Givinostat is designated an 'orphan medicine' by the EMA. It is a class I and II zinc-dependent histone deacetylase inhibitor that modulates the uncontrolled histone deacetylase activity in dystrophic muscles, which contributes to the pathology of DMD. The formulation is an oral suspension where each ml contains 8.86 mg of givinostat (as hydrochloride monohydrate). The pack size is 140 ml and administration is orally using a graduated syringe. Dosing is weight based ranging from 22.2 mg twice daily for patients who weigh

≥ 15 kg to < 20 kg up to 53.2 mg twice daily for patients with a weight ≥ 60 kg.

1. Comparative effectiveness of givinostat (Duvyzat®)

In the pivotal phase III EPIDYS clinical trial eligible participants were ambulant, male, and aged at least six years and had a genetically confirmed diagnosis of DMD. Participating boys were randomly assigned to receive either oral givinostat or matching placebo twice a day for 72 weeks, stratified by concomitant steroid use. The dose of givinostat was flexible, based on weight and was reduced if not tolerated. The starting dose was 20 mg to 70 mg oral givinostat twice daily with a reduced dose of 13 mg to 47 mg if required. Boys were divided into two groups on the basis of their baseline vastus lateralis fat fraction (VLFF; measured by magnetic resonance spectroscopy): group A comprised boys with a VLFF of more than 5% but no more than 30%, whereas group B comprised boys with a VLFF of 5% or less, or more than 30%. The primary endpoint compared the effects of givinostat and placebo on the change in results of the four-stair climb assessment between baseline and 72 weeks, in the intention-to-treat, group A population. The key secondary endpoints were the change from baseline after 72 weeks in the North Star Ambulatory Assessment (NSAA) total score, NSAA cumulative loss-of-function, time to rise, six minute walk test, knee extension, elbow flexion and vastus lateralis fat fraction (VLFF).

Some 359 male patients were assessed for eligibility and 179 were enrolled into the study. The 179 patients were randomly assigned to receive either givinostat (n=118) or placebo (n=61) and 170 completed the study. On the basis of vastus lateralis fat fraction (VLFF) 120 (67%) of the 179 participants were in group A and 59 (33%) were in group B. Baseline characteristics were similar in the givinostat and placebo groups where the median age was 9.8 years. The mean treatment duration was 493 days and compliance exceeded 98% in all groups. The primary endpoint was analysed using an analysis of covariance (ANCOVA) and as blinded four-stair climb data were not normally distributed they were log-transformed before analysis. For participants in group A the geometric least squares mean ratios for the log-transformed four-stair climb results at 72 weeks versus baseline were 1.27 in the givinostat group and 1.48 in the placebo group (ratio 0.86 (95% CI 0.75 to 0.99; p=0.035). Using the non-log-transformed data at 72 weeks the mean four-stair climb changes from baseline were 1.25 seconds in the givinostat group as compared with 3.03 seconds in the placebo group resulting in a 1.78 second slower decline with givinostat. When analysed as velocity, four-stair climb results at week 72 were 0.243 tasks per second in the givinostat group and 0.209 tasks per second in the placebo group, a least-squares mean difference of 0.034 tasks per second (p=0.029). The results of the four-stair climb assessment worsened in both groups over the

study period, however the decline was significantly smaller with givinostat than with placebo. The key secondary endpoints did not differ significantly between the treatment groups.
Additional evidence to support the efficacy and safety of givinostat therapy comes from the ongoing multicentre open-label extension study (OLE study). The fifth interim analysis of the OLE study has not yet been published. The OLE study had 207 participants including 119 patients with DMD enrolled in either the phase II trial or EPIDYS (givinostat group), 58 patients who were treated with placebo in previous givinostat studies (delayed givinostat group) and 30 givinostat naïve patients with DMD. In the OLE study there was a flexible weight-based treatment regimen with the starting dose matching what the patient received at the end of the previous givinostat study. The primary endpoint was the type, incidence and severity of treatment related and non-related adverse events and serious adverse events from baseline to week 48 and then yearly until the end of study. The descriptive analysis indicated a slower deterioration of muscle function than would be expected and suggested a delay in the occurrence of major disease milestones, including loss of ambulation. It was argued that the median age of the loss of ambulation in the OLE givinostat group (i.e 16.7 years) was considerably higher than the median age expected in a DMD population treated with corticosteroids only (11 years 8 months) based on a 2022 analysis of data from the UK North Star Network database.

The NCPE Review Group had a number of observations in relation to the clinical trial data. As DMD progresses over time individuals lose the ability to walk, followed by loss of upper limb function, respiratory decline and cardiac complications. There is no randomised controlled clinical trial (RCT) data to show that givinostat reverses any of these complications by impacting DMD disease progression. The Review Group also notes that there is no RCT data to show that givinostat reduces mortality in patients with DMD.

2. Safety of givinostat (Duvyzat®)

In the EPIDYS clinical trial adverse events occurred in 95% in the givinostat group and 93% in the placebo group. The most common adverse events with givinostat were diarrhoea (36%), vomiting (29%), nasopharyngitis (26%), headache (24%) and abdominal pain (21%). Givinostat may cause a dose-related thrombocytopenia and 67 of the 118 patients (57%) randomised to givinostat in the pivotal clinical trial experienced a reduction in platelet count as compared with 5% in the placebo group. In 33 of the 118 patients (28%) the dose of givinostat was reduced because of thrombocytopenia but there was no evidence of excessive bleeding. It is advised that blood counts be monitored every two weeks for the first two months of treatment and at month three and every three months thereafter. Givinostat may cause hypertriglyceridaemia which occurred in 23% of

patients in the pivotal trial. High triglycerides resulted in discontinuation and led to dosage modification in 2% and 8% respectively of patients treated with givinostat in the EPIDYS study. The dose of givinostat should be modified if fasting triglycerides are greater than 300 mg/dl (approximately 3.42 mmol/l) and treatment should be discontinued if triglycerides remain elevated. Givinostat can cause prolongation of the QT interval on an ECG and it should be avoided in patients who are at an increased risk for ventricular arrhythmias (including torsades de pointes) such as those with congenital long QT syndrome, coronary artery disease, electrolyte disturbance and those being treated with concomitant drugs known to cause QT prolongation e.g antiarrhythmic agents (amiodarone, quinidine) and antimicrobial agents (macrolide antibiotics).

3. Cost effectiveness of givinostat (Duvyzat®)

Methods

The economic evaluation considered the cost-effectiveness of givinostat relative to established clinical management for the treatment of boys with Duchenne muscular dystrophy (DMD) aged 6 years and older who are ambulant at treatment initiation. A cohort multi-level state transition model structure with disease – specific health states was developed in Microsoft Excel to estimate lifetime costs and quality adjusted life years (QALYs). It was based on output from Project HERCULES (Health Research Collaboration United in Leading Evidence Synthesis) an initiative led by Duchenne UK to develop tools and evidence to support Health Technology Assessment (HTA) and reimbursement decisions for new treatments for DMD.

The cost-effectiveness model assumes that all patients start in health state 1 i.e the early ambulatory health state, reflecting the inclusion criteria for the EPIDYS clinical trial. Health states 1, 2 and 3 form the ambulatory health states. Patients can transition from health state 3 to non-ambulatory health states. Patients transitioning from the first non-ambulatory state which is health state 4 may transition into one of two pathways depending on which function (hand-to-mouth function (HTMF) or independent breathing) is lost first. Whilst transition probabilities in the cost-effectiveness model may vary according to each pathway, the utilities and costs accrued in advanced health states (health states 7 and 8) are aligned. Non-ambulatory health states are defined in terms of Brooke scale of upper extremity function (Brooke score) and the forced vital capacity (FVC) score.

The primary clinical data source informing givinostat effectiveness was the EPIDYS phase III study and the associated open-label extension study (OLE) as outlined above. These also informed adverse event rates, discontinuations and dose modification inputs. For the established clinical management arm, effectiveness was assumed to follow the natural history model supplemented by UK real world

data. In the absence of comparative data for long-term outcomes, the relative efficacy of givinostat in addition to established clinical management as compared with established clinical management alone was derived using an indirect treatment comparison. As the UK real-world data and the givinostat evidence do not have a common comparator, an unanchored matching-adjusted indirect comparison (MAIC) was used to derive the relative efficacy of givinostat versus established clinical management. The NCPE Review Group highlighted the limitations with the submitted MAIC, including the lack of reported baseline characteristics for the UK real-world data. It was noted that in the submitted MAIC the cohorts were matched on just one covariate i.e age at initiation of corticosteroids. Acceleration factors were applied to both treatment arms to project median ages at unobserved disease milestones.

MAIC-adjusted Kaplan-Meier curves were extrapolated beyond the observed follow-up using the log-normal parametric survival function. The same parametric form was applied for loss of ambulation (LOA), non-invasive ventilation (NIV) and forced vital capacity less than one litre (FVC<1L) outcomes. Transition hazard ratios were further calibrated to align with the multi-cohort model structure. To estimate the proportion of givinostat patients requiring spinal fusion surgery the cost-effectiveness model assumes that the loss of ambulation hazard ratio for givinostat versus established clinical management (ECM) i.e 0.51 is applied to the scoliosis rate with ECM. The model background mortality (with no additional excess mortality) is explicitly applied beyond what is reflected in the natural history model, with life-year gains in the givinostat arm driven by delayed progression. Patient outcomes were quantified as quality-adjusted life years (QALYs).

Utility data for the base-case analysis was obtained from a study by Audhya et al. (2023) as it was considered to provide recent patient-reported EQ-5D-5L data which aligned with the health states of the cost-effectiveness model. Results in the base case represented the perspective of the Health Service Executive (HSE). A scenario incorporating the impact on caregiver health was also submitted. A discount rate of 4% was applied to costs and outcomes.

Results

Over a lifetime horizon the total discounted costs associated with givinostat amounted to €3,198,766 as compared with €104,467 for established clinical management, resulting in an incremental cost of €3,094,298. Givinostat provided a mean quality adjusted life year (QALY) gain of 3.2 resulting in an incremental cost-effectiveness ratio (ICER) of €957,911 per QALY gained (Table 1).

Table 1. Cost-effectiveness of givinostat (Duvyzat®) versus established clinical management.

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (€/QALY)
Givinostat	€3,198,766	9.1			
Established clinical management	€104,467	5.9	€3,094,298	3.2	€957,911

ICER: Incremental cost-effectiveness ratio QALY: quality adjusted life year

When caregiver health related quality of life was considered the ICER was €323,879/QALY. A price-ICER analysis indicated a price reduction of 96.1% would be required to reduce the base case ICER to the €45,000/QALY threshold. An 86.8% price reduction is required to reduce the carer QALY and informal care ICER to just under €45,000/QALY.

Sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted and resulted in an ICER of €905,318/QALY. The probability of givinostat being cost-effective at the €45,000/QALY threshold was 0%. A deterministic sensitivity analysis was also presented. The parameters with the greatest impact on the base-case ICER included the hazard ratios applied to reflect the givinostat relative treatment effect for transitions from health state 1 to 2, health state 2 to 3 and health state 3 to 4. Other parameters with an influence on the ICER included the discontinuation rates for givinostat and to a lesser extent some patient utilities. It is noted that discontinuation of givinostat on loss of ambulation improves cost-effectiveness with an ICER of €575,490/QALY.

4. Budget impact of givinostat (Duvyzat®)

A budget impact analysis was submitted to estimate the 5 year budget impact of givinostat. The total cost of a 140ml pack including relevant fees and Framework agreement rebate excluding pharmacy fees is €15,934.04. Because of weight based dosing the estimated cost per patient per annum ranges from €92,000 (for patients between 10kg to less than 12.5kg) up to €334,000 per annum for patients who weigh at or above 70kg. The eligible population was considered to increase from 50 patients in year 1 to 52 patients in year 5. When treatment discontinuations and market share were taken into

account the number of patients treated with givinostat was estimated to increase from 7 patients in year 1 to 34 patients in year 5. The estimated 5 year gross drug budget impact for givinostat is €26,120,398. If all eligible patients were treated with givinostat the 5 year gross budget impact is estimated at €58,985,754. The 5 year net drug budget impact was assumed to be similar to the 5 year gross budget impact.

Patient Organisation Submission

A patient organisation submission was received from Muscular Dystrophy Ireland.

5. Conclusion

Having considered the cost-effectiveness of givinostat (Duvyzat®) for the treatment of Duchenne muscular dystrophy in ambulant patients aged six years and older with concomitant corticosteroid treatment the NCPE recommends that givinostat not be considered for reimbursement unless cost-effectiveness can be improved*.

*This recommendation should be considered while also having regards to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.