Summary

WHAT IS DUCHENNE MUSCULAR DYSTROPHY?

Duchenne muscular dystrophy (DMD) is a genetically inherited neuromuscular disease that almost entirely affects boys and results in a progressive loss of muscle function, resulting in progressive weakness and eventual death usually from cardiac and respiratory failure. It is the most common pediatric muscular dystrophy with a prevalence of one in 3,500 - 5,000 live male births, or about 400 to 600 boys per year in the US.

TREATMENT OPTIONS

Since DMD is a degenerative disease that affects multiple organ systems, care of patients with DMD is provided by a multidisciplinary team, typically led by a neuromuscular specialist. Supportive care, such as physical and occupational therapy to maintain ambulation, is integral to management of DMD. Corticosteroids, including prednisone and **deflazacort** ([**Emflaza**®, PTC Therapeutics]), are the mainstay of therapy for DMD. Deflazacort was first licensed for use overseas in the 1980s and was approved in February 2017 for treatment of DMD in the US.

Exon-skipping therapies (**eteplirsen** [**Exondys 51**®, Sarepta]) and **golodirsen** [Investigational, Sarepta]) are a new class of drugs that may be beneficial in slowing progression of the disease. Exon-skipping therapy is intended to work by increasing production of dystrophin, the protein that is lacking in boys with DMD. Eteplirsen was approved in the US in September 2016 for patients with DMD who have mutations amenable to exon 51 skipping (about 13% of the DMD population). Golodirsen was developed for patients with mutations amenable to exon 53 skipping (estimated to be 9% of the population with DMD), and is currently under evaluation by the FDA, with an expected decision date in August 2019.

KEY REPORT FINDINGS

- For deflazacort, discounts of at least 85% from its list price would be needed to achieve commonly cited thresholds for cost-effectiveness.
- No price can be suggested as a fair value-based price for eteplirsen or golodirsen because no persuasive evidence yet exists to demonstrate the clinical effectiveness of either drug.
- As with all treatments for ultra-rare conditions, judgments of overall value require consideration of contextual issues and broader benefits for patients and families.

KEY POLICY RECOMMENDATIONS

- Patient groups and clinicians should work with manufacturers early in the design of clinical trials to embed the expectation that patient-centered outcomes will be measured in key trials, and that the company will bring an effective drug to market at a price that aligns fairly with the demonstrated benefits for patients.
- Manufacturers should balance early access with the need for fair pricing and ongoing evidence development, drugs granted accelerated approval should be priced closer to the marginal cost of production until clinical benefits are proven.
- For payers, there is no reason to require renewal criteria demonstrating the attestation of benefit for continuing deflazacort, as continued clinical decline is expected on treatment. An insurer could reasonably cover an N-of-1 trial of deflazacort versus prednisone to assess side effects in an individual patient, but this is only a consideration because of the extremely high price of deflazacort. For exon-skipping therapies, there is no reason to require attestation or other renewal criteria, as some rate of continued clinical decline is expected while on treatment, even if treatment is effective.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that deflazacort, eteplirsen, and golodirsen improve outcomes in patients with DMD?

Deflazacort: Moderate certainty of comparable or better net health benefits compared with prednisone.

Eteplirsen: There was insufficient evidence to judge the net health benefit of adding eteplirsen compared with using corticosteroids and supportive care alone.

Golodirsen: There was insufficient evidence to judge the net health benefit of adding golodirsen compared with using corticosteroids and supportive care alone.

KEY CLINICAL BENEFITS AND HARMS STUDIED IN CLINICAL TRIALS

How effective are current DMD therapies?

	Deflazacort[1]
Improved Muscle Strength	⟷ No differences
Improved Motor Function	⟷ No differences
Loss of ambulation (impaired mobility)	May be delayed (Inconclusive)
Pulmonary Function	⟷ No differences

1. Compared to Prednisone

Steroid treatment has multiple important side effects. A purported benefit of deflazacort is that it may have lower rates of certain side effects than prednisone. Rates of undesired weight gain appear to be lower with deflazacort than prednisone, but growth reduction appears to be greater with deflazacort. Cataracts may also be more common with deflazacort.

Clinical Analyses (continued)

	Eteplirsen (plus corticosteroids and supportive care)[2]	Golodirsen (plus corticosteroids and supportive care)[2]
Improved Muscle Strength	Insufficient data	No data
Improved Motor Function		
Loss of ambulation (impaired mobility)		
Pulmonary Function		
Dystrophin	↑ Small increase	↑ Small increase

2. Compared to corticosteroid and supportive care alone

Harms of the exon-skipping therapies appear to be limited. There were no AEs leading to discontinuation of the eteplirsen, and no deaths were reported. No safety data have yet been reported for golodirsen.

Clinical Analyses (continued)

SOURCES OF UNCERTAINTY

Dosing and duration of corticosteroid: Although there is evidence that corticosteroid treatment is beneficial for patients with DMD, the optimal dosing, dosing regimen, and duration of therapy remain unclear.

Evidence limitations on deflazacort: There are very few head-to-head trials of deflazacort and prednisone. The majority of the long-term data comparing the two drugs are from observational studies that may be subject to selection bias and lack consistent dosing and outcomes measures.

Evidence limitations on exon-skipping therapies: Data for exon-skipping therapies consist primarily of surrogate outcomes (e.g., dystrophin levels) from very small trials that have no validated threshold that defines meaningful clinical improvement. Furthermore, there is limited or no evidence demonstrating improvements in function.

Measurement of effectiveness: The outcomes used in clinical trials may not fully characterize the effects of drug therapy, as there appears to be a gap between currently reported trial outcomes and the experiences of patients as observed and reported by their caregivers.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

At the annual net price of $81,400, deflazacort exceeds commonly accepted thresholds for cost-effectiveness of $50,000-$150,000 per quality-adjusted life year (QALY) gained or per life-year (LY) gained when compared to prednisone. Under modeling assumptions that were felt to be very favorable to deflazacort results showed:

	Deflazacort
Cost per QALY gained	$663,000
Cost per LY gained	$632,000

In the absence of adequate evidence demonstrating clinical benefits of eteplirsen, we examined whether eteplirsen would be cost effective under extreme assumptions such as having it restore all patients with DMD to perfect health for an additional 40 years of life. At its current annual cost of $1,002,000, under this extreme assumption eteplirsen would still have a cost per QALY gained of $1,110,000 and a cost per LY gained of $1,450,000, far exceeding commonly accepted thresholds for cost-effectiveness.

Economic Analyses (continued)

VALUE BASED PRICE BENCHMARKS (UNDER MODELING ASSUMPTIONS THAT WERE FELT TO BE VERY FAVORABLE TO DEFLAZACORT)

What is a fair price for deflazacort based on its value to patients and the health care system?

	Deflazacort
Annual List Price[3]	$117,400
Net Price	$81,400
Annual Price to Achieve $100,000-$150,000/QALY Threshold	$10,880-$17,140
Discount from List Price Required to Reach Threshold Prices	85%-91%
Net price within range?	NO

3. Wholesale acquisition cost (WAC), prior to any discounts or rebates; Price per year is for a 40 kg patient

These value-based price benchmarks (VBPBs) were under modeling assumptions that were felt to be very favorable to deflazacort, so the above results can be considered upper bounds on a value-based price.

VBPBs could not be calculated for eteplirsen or golodirsen in the absence of adequate evidence demonstrating clinical benefits

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

The potential budget impact analyses for deflazacort were not updated for the corrected report posted on April 22, 2022, as deflazacort was approved by the Food and Drug Administration in 2017 and given the Report version posted on August 15, 2019 did not identify budget impact findings at list pricing (or other pricing) that were above the budget impact threshold. ICER typically does not assess the potential budget impact of treatments that have been in use in clinical practice for more than two years.

We did not estimate the budget impact of eteplirsen and golodirsen in the absence of adequate evidence demonstrating clinical benefits.

Voting Results

The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on July 25, 2019. The results of the votes are presented below. More detail on the voting results is provided in the full report.

CLINICAL EVIDENCE

- A majority of panelists did find adequate evidence to support a net health benefit of deflazacort over prednisone.
- The panel did not find sufficient evidence to show a net health benefit of eteplirsen or golodirsen added to corticosteroids and supportive care versus corticosteroids and supportive care alone.

LONG-TERM VALUE FOR MONEY

- A majority of panelists found that deflazacort and eteplirsen provide a low long-term value for money. There was no vote on golodirsen because a price has not yet been established.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- Before voting on value, panel members weighed the therapies' other benefits and contextual considerations. A majority of the panel found that all three therapies treat conditions of high severity and a high lifetime burden of illness.
- The majority of the panel also found that deflazacort could significantly reduce caregiver or broader family burden.
- The panel found there is significant uncertainty about the magnitude or durability of the long-term benefits of eteplirsen and golodirsen.

Policy Recommendations

For Payers

- Given the substantial remaining uncertainty regarding the benefits of these treatments in certain subpopulations and their high cost, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use. Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. For deflazacort, failure on prednisone is based on toxicity, and so a step therapy policy should not require a fixed period of time for a trial of prednisone but rather documentation of adverse effects.

- In terms of renewal criteria, there is no reason to require attestation of benefit for continuing deflazacort, as continued clinical decline is expected on treatment. An insurer could reasonably cover an N-of-1 trial of deflazacort versus prednisone to assess side effects in an individual patient, but this is only a consideration because of the extremely high price of deflazacort. For exon-skipping therapies, there is no reason to require attestation or other renewal criteria, as some rate of continued clinical decline is expected while on treatment, even if treatment is effective.

For Manufacturers:

- To balance early access with the need for fair pricing and ongoing evidence development, drugs granted accelerated approval should be priced closer to the marginal cost of production until clinical benefits are proven.

- Manufacturers and clinical researchers should follow the example of work being done by Casimir to develop better outcome measures that increase the likelihood of detecting the effects of treatments on patient-important outcomes.

- Manufacturers and clinical researchers should consider ways to perform objective assessments in a home setting rather than requiring young patients with DMD to travel long distances prior to testing.

For Patient Groups and Clinicians

- If manufacturers are abdicating their responsibilities to provide adequate evidence for new therapies and/or are charging excessive prices for treatments, patient groups and clinicians must use their moral standing to apply pressure by speaking up.

- Patient groups and clinicians should work with manufacturers early in the design of clinical trials to embed the expectation that patient-centered outcomes will be measured in key trials and that the company will bring an effective drug to market at a price that aligns fairly with the demonstrated benefits for patients.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).