June 18, 2019

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On behalf of Parent Project Muscular Dystrophy (PPMD) and the Duchenne community, we appreciate the opportunity to again offer feedback on *ICER Deflazacort, Eteplirsen, and Golodirsen for Duchenne Muscular Dystrophy: Effectiveness and Value*. As we have stated previously, we believe that it is imperative that the framework ICER constructs for the valuation of these – and emerging – Duchenne products be specific to Duchenne and reflective of Duchenne expert input. While the report does reflect some of these inputs, there remain additional areas of clarification needed in order for the foundational understanding of Duchenne and the framework upon which the modeling is built to reflect the Duchenne community’s experience and the input provided to date. We remain concerned that the report fails to reflect that – within the Duchenne community - slowing or halting of disease progression through treatment intervention is significant. The impact of such - on the lives of both patients and caregivers - should be reflected in the modeling.

PPMD’s concerns are focused specifically on the following areas:

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<th>Concern about the ICER Assessment Timing for Products Approved via the Accelerated Approval Pathway</th>
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The FDA Accelerated Approval Program was established in 1992 to allow for products that meet regulatory rigor based on efficacy of a surrogate endpoint that is reasonably likely to have clinical benefit for select patient communities in which there is significant unmet need. By definition, limited clinical data for products approved through accelerated approval will exist at the time of approval and in early stages of the phase IV environment. In these circumstances, this lack of clinical data is not a reflection of the robustness of the therapy, but rather the regulatory review pathway agreed upon by the product developer and the Food and Drug Administration.

PPMD has articulated our concern about the timing of ICER’s assessment for products approved utilizing this pathway in several occasions: a) In November of 2015 and including our formal engagements as a member of the working group at the ICER Orphan

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Drug Assessment & Pricing Summit; b) in our 2 public comments regarding “Modifications to the ICER value assessment framework for treatments for ultra-rare diseases” (November 2017) and; c) our series of engagements surrounding the current Duchenne-product specific ICER assessment now underway.

We remain concerned about the lack of available clinical data that may potentially impact the ability to perform an appropriate value assessment. Eteplirsen was approved utilizing the Accelerated Approval pathway on the surrogate outcome measure of dystrophin, and Golodirsen is utilizing the accelerated approval pathway, and is not yet approved. Thus, the valuation of these products is compromised as the ICER Evidence Rating Matrix is dependent upon the availability of clinical data including data on long term outcomes and the level of certainty in the evidence. In the case of these products, this lack of data may not necessarily be a reflection of the robustness of the therapy, but rather the regulatory review pathway agreed upon by the sponsor and the FDA.

Concerns regarding the ICER economic model structure, assumptions, and input parameters

Concerns about the Model Structure
The selection of the partitioned survival model structure to model DMD is inappropriate, since this framework typically models a cohort of patient through time as they move between a set of exhaustive and mutually exclusive health states. This modeling framework is not reflective of the natural progression of the Duchenne disease state, since in DMD the health states are not mutually exclusive from one another. In fact, the patients experience each health state in a consecutive linear manner, where the current health state is dependent on the previous state.

Concerns about the Model Assumptions
Concerns about the Duchenne disease states assumptions

• It is critical that Duchenne disease progression be understood to be more nuanced than the overly-simplistic assumption of three disease stages of “ambulatory”, “non-ambulatory”, and “death” in the current draft report.

• Both the Duchenne Regulatory Science Consortia (D-RSC) of the Critical Path Institute https://c-path.org/programs/d-rsc/ has established a disease progression model that includes 6 stages of Duchenne progression (this model is incorporated into the Project HERCULES HE model):
  o Ambulatory: Early ambulatory, late ambulatory: Intermediate;
  o Non-Ambulatory: Early Non-ambulatory (Brooke 1), Late non-ambulatory (Brooke 2-4), Late non-ambulatory (Brooke 5)
Concerns about the Key Model Assumptions Outlined in Table 4.1

**Assumption:** Treatment effects were modeled as rightward shifts of the survival curves for losing ambulation and death and/or if there was evidence of having different rates of SAEs.
**Comment:** It is possible that a SAE may not influence the rightward/leftward shift of the survival curve in instances where the AE experienced does not impact ambulation. A common example would include behavioral side effects.

**Assumption:** Patients on prednisone transitioned between “ambulatory,” “non-ambulatory,” and “death” health states following the survival curves originally projected in a prior analysis, which was based on international clinical trial data and historical data for patients diagnosed with DMD and receiving steroids.
**Comment:** This is an oversimplification of the real-world experience of Duchenne patients and does not reflect current community consensus around the Duchenne disease progression model as being led by coalitions such as the Critical Path Institute’s Duchenne Regulatory Science Consortium (D-RSC) and Project HERCULES.

**Assumption:** Hence, the relative proportion of ambulatory patients in early and late ambulation and in early and late non-ambulation after losing ambulation is assumed to be the same in all treatments.
**Comment:** Assuming that the proportion of early/late ambulatory and early/late non-ambulatory patients is the same across treatment may be an oversimplification. This is the case because even with steroids (i.e., prednisone and deflazacort), the proportion of patients who can tolerate these 2 drugs are very different. By tolerance alone, if let's say a lot of patients discontinue prednisone by a higher number at the early ambulatory state than those who are on deflazacort, this could potentially impact the proportion of patients in early/late ambulation who are going to be in prednisone or deflazacort.

**Assumption:** The proportion of supportive care costs from a societal perspective made up by supportive care costs from a health care sector perspective was the same in the ambulatory and non-ambulatory health states.
**Comment:** While evidence development around caregiver spillover in Duchenne is in nascent stages, the impact of progression in relationship to the need for increasing supportive care needs has been well established. To date several Burden of Disease studies have been conducted in Duchenne yielding similar overall economic analyses. In
the study by Landfeldt et al., an international data set from the Treat NMD Registry utilized data from Germany, Italy, the United Kingdom, and the United States. Mean per-patient annual direct cost of illness was 7 to 16 times higher than the mean per capita health expenditure in these countries. In addition to direct costs, Duchenne was also associated with large productivity losses, for both patients and caregivers. This study further stratified costs across the progression of the disease and found that households caring for a boy with Duchenne carry a large economic burden that increases markedly with disease progression. It should be noted that outcomes for only one primary caregiver were included in these calculations and thus these estimates will be underestimates for the majority of families in which additional family members (second parent, grandparent, sibling, etc) contribute to the informal care of the individual with Duchenne. For this reason, the existing Burden of Disease study results should be considered conservative. In addition – in 2018 PPMD conducted an externally-led Patient Focused Drug Development meeting in collaboration with the FDA and other federal agency partners. Throughout the meeting panels stratified by disease stage testified and live polling was conducted, including questions intended to assess resource gaps, disease burden, and economic impact of Duchenne. The full data set from the Compass meeting polling, as well as the Compass meeting white paper, a downloadable pdf of this report, and the recording of the live stream from the meeting are available at: https://www.parentprojectmd.org/advocacy/our-strategy-and-impact/regulatory-advocacy/

Assumption: Patients are diagnosed and begin treatment at five years of age.  
Comment: Emflaza is commercially available to patients ages 24 months and older.

Assumption: SAEs (weight gain, cushingoid, fractures, cataracts) related to prednisone and deflazacort resulted in a disutility of 0.05.  
Comment: We believe that additional side effects that have been demonstrated to have significant impact on patients’ drug tolerance, health, and quality of life should also be considered. Side effects that should be considered include:

- Neurodevelopmental considerations - certain genetic variants associated with DMD are now known to result in atypical dystrophin expression in the brain
- Fracture-induced Fatty Embolism Syndrome
- Diminished or halted linear growth, and impacts on self-image

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2 The burden of Duchenne muscular dystrophy An international, cross-sectional study  
Erik Landfeldt, Peter Lindgren, Christopher F. Bell, Claude Schmitt, Michela Guglieri, Volker Straub, Hanns Lochmüller, Katharine Bushby First published July 2, 2014, DOI:  
https://doi.org/10.1212/WNL.0000000000000669
Lack of assumption and modeling of the impact of adverse effects (AEs) of long term corticosteroid use:

- Since patients with DMD are typically on corticosteroids on a long term basis and gain weight and lose muscle mass at the same time, this will potentially impact ambulation and functional activities of daily living. We suggest ICER incorporate the modeling of the impact of major weight gain from steroid use as an AE.

Assumption: In establishing the survival curve, the model assumed that treatments may extend time to loss of ambulation, but they did not change the proportion of time spent in “early” versus “late” ambulation, and similarly affected the non-ambulatory state.

Comment: If treatment is assumed to extend time to loss ambulation, then the proportion of patients in early ambulation would be higher than the proportion of patients in late ambulation compared to the group that do not have treatment. Thus, this assumption over simplifies the DMD disease complexity and potential drug effect.

Concerns about the Transition Probabilities and Input Parameters
Most of the transition probabilities and key model inputs have been extracted from an ongoing project, a scientific poster, and a single study. PPMD is concerned that the use of the transition probabilities, and key costs and utility estimates from limited sources impacts the credibility of the model results.

In Conclusion
We thank ICER for the opportunity to participate in this review. We believe that the above expressed concerns may raise questions about the credibility of the cost-effectiveness model results among all stakeholders. It is our hope that our comments will be taken into consideration and that ICER’s framework serves to further inform and enhance – rather than hinder – our Duchenne therapy development landscape. Please contact Annie Kennedy, SVP – Legislation & Policy at annie@parentprojectmd.org for any additional information.

Sincerely,

[Signature]

Founding President & CEO, Parent Project Muscular Dystrophy