THE LAST WORD:

Treatments for Myasthenia Gravis: Effectiveness and Value
ICER's Final Evidence Report
Issued October 20, 2021

On October 20, 2021, ICER issued its Final Evidence Report on two treatments – one FDA-approved, the other awaiting approval – for myasthenia gravis. After following its typical process, including the release of a draft report, solicitation of public comments, and a public meeting, ICER determined that both treatments "significantly improve function and quality of life" for patients suffering from generalized myasthenia gravis. Yet, despite their clinical effectiveness, the report concluded that both drugs were likely overpriced and recommended steep discounts for payers and insurers. Given the inherent shortcomings of ICER's process and methodologies, most of the conclusions in this report should not be taken seriously.

Myasthenia gravis (MG) is an autoimmune disease resulting from antibodies that block or destroy nicotinic acetylcholine receptors at the neuromuscular junction. Its most common symptoms include varying degrees of skeletal muscle weakness. In the U.S. there are as many 60,000 known cases of MG, but, because it often remains undiagnosed, the prevalence is likely much higher.

ICER's final evidence report purports to review the clinical and cost-effectiveness of two specific MG therapies:

- **Eculizumab (Soliris®)** – Alexion: A monoclonal antibody treatment approved by the FDA in 2017.
- **Efgartigimod** – argenx: An immunoglobulin fragment treatment currently awaiting FDA approval. A decision on the latter is expected in mid-December 2021.

As always, ICER believes its main contributions to the discussion of MG treatments are its Health-Benefit Price Benchmarks (HBPB), the pricing ranges at which ICER claims a drug can be considered cost-effective. These benchmarks are based on their assumption that the "threshold" value of a year in perfect health – expressed as a cost per quality-adjusted life year (QALY) – ranges from $100,000 to $150,000.

ICER recommended the following HBPBs for the two MG treatments:

- **Eculizumab**: $13,200-$19,400/year (would require a discount of at least 97% off current U.S. list price)
- **Efgartigimod**: $18,000-$28,400/year (discount not presented because the report used a placeholder price)

These findings are problematic for many reasons. For one, ICER's assumption-driven simulation models do not adequately consider the

perspectives of patients when assessing the value of the treatments. When patients consider the value of a new therapy, they consider many factors – productivity, employment options, impact on home/work life, burdens on caregivers, and improvements relative to prior treatments just to name a few. And, some conditions – MG among them – have disparate impacts on specific demographic cohorts. Yet, none of these factors are given significant consideration in either the clinical or cost analyses in the report. While some are acknowledged, they have no real impact on the models or inputs ICER uses to reach its conclusion. This is a major shortcoming of virtually all ICER's drug evaluations.

In this particular report, ICER's primary model focuses on three health states: improved MG on treatment, unimproved MG on treatment, and unimproved MG off treatment. For a disease like MG, which can negatively impact patients in a wide variety of ways, such a simplistic model cannot adequately summarize all the clinical or quality-of-life factors that are important to patients. There are also more fundamental problems with the instruments ICER uses to measure patient progress. More on that below.

Another problem with ICER's approach is that, while it is myopically focused on clinical data over patients and their needs, the data used in the report does not reflect the clinical reality of treating MG patients. While ICER does incorporate some MG-specific instruments to measure outcomes and effectiveness, those instruments are not uniformly used by doctors prescribing MG treatments. In addition, ICER uses bootstrapping methodologies to convert data from clinical trials – inherently limited in scope and purpose – to make broader claims about the treatments' clinical and cost effectiveness. Obviously, when analyzing newer treatments, data can often be limited to whatever is gathered during clinical trials. But the lack of available evidence does not justify the invention of new evidence to fill in the gap. As usual, ICER tends to downplay the impact their extrapolations will likely have on the accuracy of their assessments.

Finally, ICER's use of the quality adjusted life year (QALY) as their baseline measurement to assess treatment values continues to cast doubt on their entire modeling approach.

As many have noted, the QALY standard inherently discriminates against patients with disabilities or those suffering from chronic or long-term conditions like MG. For many patients with a chronic condition, a "year in perfect health" is not a realistic standard. As a result, any value estimate based on this standard will automatically devalue treatments for these patients. The proof is in the results: To date, every rare disease therapy assessed by ICER – which now includes MG – has met with negative recommendations, including those shown to have significant – even life-altering – clinical benefits.

Setting fairness and discrimination concerns aside, ICER's use of the QALY standard – along with the models it uses to measure patient outcomes – is an analytical and scientific dead end, something observers have noted for years. The analyses in ICER's reports are centered on assumption-driven simulation models to support cost-per-QALY claims for threshold pricing recommendations. By design, any claims produced by this framework cannot be empirically evaluated. That being the case, ICER's methods fail to meet even the most basic standards of normal science.

Case in point, in the MG report, ICER performs a hypothetical, assumption-driven simulation on an imaginary patient population by mapping scores from an MG-specific clinical instrument – the Quantitative Myasthenia Gravis (QMG) – to the EQ-5D-5L, a broader health-status descriptor. But the very nature of the QMG makes this task mathematically impossible.

The QMG is a 13-item scale used to quantify disease severity in myasthenia gravis. It measures ocular, bulbar, respiratory, and limb function, grading each finding, and ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits) by collapsing these various scores to a single value. It is an ordinal multivariate score which ranks respondents by the presence and severity of the disease. In other words, the QMG can compare patients' change in rank on the ordinal scale, but, unlike a ratio score, it cannot measure the difference in value between disease states following a new therapy intervention. Therefore, it cannot be used in any analysis that involves even the most basic mathematic operation: addition, subtraction, multiplication, or division. As such, it cannot serve as the basis for mapping to a preference score.

Even if it were possible to accurately map the QMG to another instrument, the EQ-5D-5L also produces purely ordinal scores in a range that does not include an absolute zero. Indeed, roughly one-fifth of the health states that can be valued by the EQ-5D-5L yield a negative score, or a state worse than death. To put it more simply, these instruments – and the analysis ICER purports to perform with them – cannot be used to perform a scientifically credible value assessment.

And, because ICER's model is entirely driven by assumptions, it is only one out of potentially hundreds of others that could be used to supposedly evaluate MG treatments. Each model would come with its own recommendations and could even be reverse engineered to produce wholly different outcomes.

Of course, none of these concerns are new or unique to the most recent final evidence report. ICER's failures with regard to MG are merely the latest in a long line of results that cannot withstand even the most basic scrutiny. ICER is perfectly aware of these shortcomings, yet it continues to either ignore or brush criticisms aside. If ICER was simply a think tank, these failures would be largely inconsequential. However, as more healthcare decisionmakers in both the private and public sectors give more weight to ICER's imaginary recommendations, the stakes are continually being raised.

If access to or coverage for a treatment is denied on the basis of bad science and impossible math, it is the patients – not the pharmaceutical companies, insurers, or government programs – who will suffer most.