



March 16, 2020

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Comments on the Draft Evidence Report titled “Modulator Treatments for Cystic Fibrosis: Effectiveness and Value”

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide comments regarding ICER’s draft evidence report, “Modulator Treatments for Cystic Fibrosis: Effectiveness and Value,” dated February 20, 2020.

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient-centered care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of health care providers committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

Draft Evidence Report Comments

Cystic fibrosis affects 30,000 people in the United States. It is a progressive genetic disease that causes persistent lung infections and is associated with co-morbidities that include pancreatic insufficiency, sinus disease, pulmonary infection, asthma, diabetes, bronchiectasis and depression.¹ Cystic fibrosis patients experience increased hospitalization rates, life-threatening complications and a shortened lifespan – the median age of death for a person diagnosed with cystic fibrosis in the United States is 27 years.²

Managing the disease requires patients to endure a time-consuming regimen of medicines, chest physiotherapy and nebulizers. This daily regimen is not only costly, but also materially reduces

¹ Hassan M, Bonafede MM, Limone B, Hodgkins P and Sawicki G (2016) “The Burden of Cystic Fibrosis: Pulmonary Exacerbations and Health Care Resource Utilization in a Commercially Insured Population in the United States” *Value in Health* 19.

² Becker CC, Clements K, DeLong K, Harrow B, and O’Sullivan A (2011) “Economic Burden on Cystic Fibrosis in the U.S.: Costs of Care by Disease Severity and Age” *Value in Health* 14.

patients' quality of life and their school or workplace productivity. The same is true for caregivers. Medicines that are both efficacious and well tolerated will reduce these costs and, consequently, are highly valued by the patient community.

As noted in the draft evidence report, two classes of modulator drugs treat cystic fibrosis: potentiators and CFTR correctors. Ivacaftor is the only potentiator drug available. Lumacaftor, tezacaftor, and elexacaftor fall into the CFTR corrector class. The efficacy of the two classes of drugs generally increases when they are used in combination. As highlighted in the report, the FDA has approved three combination therapies. The most recent is also the only triple combination medicine, elexacaftor/ivacaftor/tezacaftor. The draft evidence report evaluates this triple-combination therapy and also updates past reviews of the three prior therapies.

IfPA has serious concerns, however, that the estimated cost-effectiveness results are inaccurate. The report applies a flawed and inapplicable methodology that significantly undervalues the benefits patients receive from these therapies, particularly triple-combination therapy.

Evidence Ratings Fail to Account for the Triple-Combination Therapy's Originality and the Fact that Cystic Fibrosis Is a Rare Disease

ICER's evidence ratings are not objective measures. Rather, the ratings reflect researchers' judgement regarding two attributes: (1) the estimated clinical benefit of the drug; and, (2) how certain the researchers are of the drug's clinical benefit. The scores are, consequently, ICER researchers' subjective assessment of the existing evidence.

In this case, the draft evidence report acknowledges that, based on the evidence, all of the combination drugs under consideration improved patient outcomes. The report also notes that the adverse side effects from the medicines were mild and uncommon. It is reasonable to conclude that efficacious medicines with minimal side effects should be rated highly. Yet the draft evidence report instead assigns triple-combination therapy a B+ and C++ evidence rating for two of the comparisons.

The report justifies these subjective ratings by noting, several times, that there are insufficient published randomized trials or observational data for triple-combination therapy in the relevant populations. In short, the available data is encouraging, but relatively little of that data is available at this point. As ICER surely realizes, there is limited data about triple-combination therapy because cystic fibrosis is a rare disease and because the drug was approved by the FDA only as of October 2019. The draft evidence report's low assessment of triple-combination therapy, therefore, essentially penalizes the treatment for being a new orphan drug that treats a rare disease.

Triple-combination therapy was granted orphan drug status by the FDA's Office of Orphan Products Development to encourage the development of treatments for cystic fibrosis. By failing to acknowledge the reality of new orphan drugs, the draft evidence report undermines the important goals of the orphan drug program. ICER's subjective assessment is particularly troubling because a low evidence rating could suggest that the drug is less effective. Not only is there no evidence to justify such a supposition, there is ample reason to expect that triple-combination therapy will provide a significant benefit to many cystic fibrosis patients. In sum, the low evidence rating is inappropriate and could unjustifiably reduce patients' access to triple-combination therapy.

The Draft Evidence Report Fails to Account for the Benefits of Expanding the Treatable Population

Treating cystic fibrosis is challenging because the disease is caused by thousands of different rearrangements in a person's genetic code. Due to this complexity, the available combination therapies before triple-combination therapy, which were all major treatment advancements, could treat only a minority of patients. Lumacaftor/ivacaftor, for example, benefits only about 40% of patients.³

Triple-combination therapy, according to the FDA, expands the treatable population to approximately 90% of cystic fibrosis patients.⁴ There is tremendous value in this advance. The FDA, in its October 21, 2019 press release affirmed that triple-combination therapy makes:

...a novel treatment available to most cystic fibrosis patients, including adolescents, who previously had no options and giving others in the cystic fibrosis community access to an additional effective therapy," said acting FDA Commissioner Ned Sharpless, M.D. "In the past few years, we have seen remarkable breakthroughs in therapies to treat cystic fibrosis and improve patients' quality of life, yet many subgroups of cystic fibrosis patients did not have approved treatment options. ***That's why we used all available programs, including Priority Review, Fast Track, Breakthrough Therapy, and orphan drug designation, to help advance today's approval in the most efficient manner possible***, while also adhering to our high standards. (emphasis added)

The FDA used "all available programs" to expedite triple-combination therapy's approval for a reason. Expanding the share of patients with an effective treatment to 90% of the population is a significant benefit. The draft evidence report fails to demonstrate that the analysis considered these benefits when evaluating triple-combination therapy, which is particularly concerning with respect to the cost-effectiveness models. Without accounting for the expansion of patients who now have an effective treatment, the cost-effectiveness models are, by design, undervaluing triple-combination therapy.

The Long-term Cost Effectiveness Model Ignores Unquantifiable Benefits

Medications that more effectively manage a disease create both quantifiable and unquantifiable benefits for patients. The methodology behind the long-term cost effectiveness models focus mostly on the quantifiable benefits. The unquantifiable benefits are, to a large extent, excluded from the analysis. Excluding these benefits biases the results toward undervaluing the medicines – the larger the number of unquantifiable benefits excluded, the more the results are undervalued.

The draft evidence report acknowledges this problem by stating that "economic models such as the ones used in this analysis cannot capture the full range of quality-of-life effects associated with

³ See Cystic Fibrosis News Today: <https://cysticfibrosisnewstoday.com/2018/09/24/vertex-and-treating-cf-costs-can-unsettle-but-vertex-remains-close-to-community-interview-series/>.

⁴ (2019) "FDA approves new breakthrough therapy for cystic fibrosis. Treatment approved for approximately 90% of patients with cystic fibrosis, many of whom had no approved therapeutic options" *FDA Press Release*, October 21; <https://www.fda.gov/news-events/press-announcements/fda-approves-new-breakthrough-therapy-cystic-fibrosis>.

the disease, or the improvements in quality of life experienced by CF patients taking CFTR modulator therapy.”

Quality-of-life measures are difficult, but important, to quantify. Cystic fibrosis patients generally rate their quality of life as low,⁵ and they highly value medicines that can reduce their daily burdens and increase their quality of life – even small improvements to their quality of life are valued highly. Since the economic models fail to capture these important unquantifiable benefits, the long-term cost-effectiveness calculation significantly undervalues the benefit these treatments offer patients.

The QALY Methodology Is Inappropriate for Rare Diseases

According to the draft evidence report, “the primary health outcome was quality-adjusted life years (QALYs) but we also report life expectancy in life years (LYs), equal value life years gained (evLYGs) and the lifetime number of acute pulmonary exacerbations.” While reporting on other factors is a positive development, the “primary health outcome” drives the conclusions drawn from the report. QALYs have well-documented weaknesses, particularly for rare diseases, that make this methodology inappropriate for evaluating the cost effectiveness of cystic fibrosis medications.

As evidence of these weaknesses, a recent report by the Pioneer Institute argues that the use of QALYs may violate several legal provisions of the Americans with Disability Act (ADA). In the study, the authors argue that:

QALY would be extremely vulnerable to challenge under the ADA if it is utilized to determine treatments available to Medicaid patients because the use of QALYs has the potential to cause state governments to administer Medicaid to disabled persons in a discriminatory manner by providing them lesser benefits by prioritizing the achievement of “asymptomatic” status, rather than “medical effectiveness.” This outcome, which would have a disparate impact on individuals with both physical and mental disabilities, would be a clear violation of the ADA.⁶

In addition to the concerns that the use of QALY methodology violates the ADA, there is also concern that QALY methodology discriminates against people with rare diseases.⁷ Rare diseases, by definition, have limited clinical trial data. These data limitations bias the results toward undervaluing the medicines and inject an excessive amount of uncertainty regarding the accuracy of the QALY estimates. Consequently, QALYs are particularly inappropriate for determining the value of cystic fibrosis treatments.

Another relevant concern about QALY methodology underscores why it is inappropriate for evaluating cystic fibrosis treatments. People living with cystic fibrosis have severely restricted lung function that reduces their endurance. Patients have indicated that clinically small

⁵ Uchmanowicz I, Jankowska-Polańska B, Rosińczuk J, Wleklík M (2015) “Health-related quality of life of patients suffering from cystic fibrosis” *Adv Clin Exp Med*. Jan-Feb; 24(1):147-52; <https://www.ncbi.nlm.nih.gov/pubmed/25923099>

⁶ McKenna J and Smith W (2020) “The Legality of QALY under the ADA” *Pioneer Institute*, February; <https://pioneerinstitute.org/featured/new-report-legal-analysis-suggests-icers-quality-adjusted-life-years-methodology-violates-the-americans-with-disabilities-act/>.

⁷ Pearson I, Rothwell B, Olaye A, and Knight C (2018) “Economic Modeling Considerations for Rare Diseases” *Value in Health* 21: 515-524.

improvements in their lung function can meaningfully improve their quality of life. QALYs, however, are designed to undervalue improvements that may be clinically small, even if they are meaningful for patients in everyday life.

Beyond these foundational problems with QALY methodology, the draft evidence report also inconsistently applies the QALY methodology by using a lower range for the cost-effectiveness threshold for triple-combination therapy (\$50,000-\$200,000 per QALY) than for two other therapies evaluated (\$50,000-\$500,000 per QALY). There is no sound justification for using a different cost-effectiveness threshold across medicines that treat the same patient population.

Conclusion

Cystic fibrosis is a devastating disease that severely restricts patients' quality of life and is associated with a shorter lifespan. The economic costs for managing cystic fibrosis are high. According to the American Thoracic Society, the average cost of care for cystic fibrosis was \$48,000 in 2006. A good deal of these costs are costs associated with hospitalization.

These are the average costs, however, and the burden for patients diagnosed with severe cystic fibrosis can be much higher. According to a 2011 study, the annual costs for patients with mild disease severity are \$30,000, but the annual costs incurred by patients who are diagnosed with severe cystic fibrosis are much higher – \$215,000.⁸ Younger patients diagnosed with severe cystic fibrosis incur even higher annual costs. Patients aged 10 to 14 with severe cystic fibrosis were estimated to be as high as \$343,900.⁹

Prior to the approval of triple-combination therapy, most patients living with cystic fibrosis did not have access to an effective treatment. Now, widely effective triple-combination therapy has generated tremendous excitement and hope in the patient community. It is critical that ICER acknowledge the value that a broadly effective treatment offers to patients.

Based on the concerns raised above, IfPA is concerned that the draft evidence report significantly undervalues these cystic fibrosis medications, particularly triple-combination therapy. If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,



Brian Kennedy
Executive Director

⁸ Becker CC, Clements K, DeLong K, Harrow B, and O'Sullivan A (2011) "Economic Burden on Cystic Fibrosis in the U.S.: Costs of Care by Disease Severity and Age" *Value in Health* 14.

⁹ Ibid.