Submitted electronically to: publiccomments@icer-review.org

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Dear Dr. Pearson:

On behalf of the Institute for Patient Access (IfPA), I thank you for the opportunity to provide comments regarding ICER’s Draft Background and Scope Document titled, “Modulator Treatments for Cystic Fibrosis: Effectiveness and Value,” released September 30, 2019.

IfPA urges ICER, as part of its evaluation of the new triple therapy that adds “the novel agent elexacaftor to the combination of tezacaftor and ivacaftor,” to adjust its cost-effectiveness methodology to account for the following realities with respect to cystic fibrosis:

- Cystic fibrosis imposes a significant burden on patients and caregivers.
- Cystic fibrosis is a rare disease. As has been well established in the literature, the QALY’s weaknesses are amplified when evaluating medicines for rare diseases.
- With respect to rare diseases, there are no definitive studies that justify either ICER’s typical cost-effectiveness threshold, or its adjusted threshold, as the appropriate benchmark for judging the cost effectiveness of a medicine.
- Due to the substantial social and economic costs imposed on patients living with cystic fibrosis, ICER’s evaluation should directly include the reduction in these costs as a quantified benefit.

The remainder of this letter provides a more detailed discussion of these issues.

Cystic Fibrosis Is a Devastating & Multifaceted Disease

Evaluating treatments for cystic fibrosis first demands a thorough appreciation for the lifetime burden of the fatal disease. Cystic fibrosis is a progressive genetic disease affecting 30,000 people in the United States. Cystic fibrosis causes persistent lung infections, wears on other organs, and is associated with a long list of co-morbidities including pancreatic insufficiency, sinus disease, pulmonary infection, asthma, diabetes, bronchiectasis and depression. It burdens both patients and their caregivers.

Patients living with cystic fibrosis often experience increased hospitalization rates and life-threatening complications. They can expect a shortened lifespan, as the median age of death of a person diagnosed with cystic fibrosis in the U.S. is 27 years. Living with cystic fibrosis also imposes a heavy day-to-day burden on patients. Managing the disease requires a time-consuming
daily regimen that typically includes medicines, chest physiotherapy and nebulizers.

Treating cystic fibrosis is complex, because the disease is caused by thousands of different rearrangements in a person’s genetic code. The current CFTR modulators, which marked a major treatment advancement, treat only a minority of patients. Lumacaftor/ivacaftor, for example, benefits only about 40 percent of patients.iii

By adding elexacaftor to the combination of tezacaftor and ivacaftor, the forthcoming treatment is expected to bring the proportion of treatable cystic fibrosis mutations to account for approximately 90 percent of cystic fibrosis patients.iv Expanding treatment from a minority of patients to the vast majority is a major advancement that will provide tremendous value to the cystic fibrosis patient community.

**QALYs Are Inappropriate for Evaluating Rare Diseases**

The well-known weaknesses of the QALY methodology make it inappropriate to evaluate the cost-effectiveness evaluation of rare diseases like cystic fibrosis.

Noting these weaknesses, Pearson et al. (2018) stated that measures like QALYs “may not be sensitive to the severity of rare diseases. This may be explained by the smaller populations with severe disease and by the proportionally smaller improvements in health outcomes that in turn generate smaller QALY gains than would be the case in larger, healthier populations. In addition, the assumption that a QALY is of equal value, irrespective of indication, may not adequately reflect societal preferences for the treatment of life-limiting rare diseases.iv

Another concern is the quality of the data. As is well known, the clinical trial data for rare diseases like cystic fibrosis are limited, as are the data on the direct and indirect cost burden. Due to these data limitations, the long-term impact on patients from the new combination therapy is uncertain. By definition, since the long-term impact is uncertain, so will be the results of the cost-effectiveness evaluation. Applying the precise QALY measurement in these circumstances creates unnecessary risks for patients’ access to medicines that can improve their quality of life.

The QALY methodology raises another concern for cystic fibrosis patients. People living with cystic fibrosis have severely reduced lung function that reduces their endurance, and patients have indicated that improvements in their lung function, even if they are clinically small, can have a meaningful impact on their quality of life. QALYs are designed to undervalue improvements that may be clinically small, even if they are meaningful for patients in practice. Therefore, using the QALY methodology will likely undervalue the benefit of this treatment to patients.

The draft scoping document attempts to address these by including equal value life years gained (evLYG) measure and adjusting the dollar cost thresholds (discussed below). The evLYG measure does not overcome the weaknesses of the QALY methodology with respect to rare diseases.

Consequently, we urge ICER to adopt alternative value approaches when evaluating the cost effectiveness of the triple combination therapy. In particular, ICER should rely on condition-specific assessments for cystic fibrosis to determine the value of the combination therapy.

**ICER Should Consider Adjusting the Cost-Effectiveness Threshold**

The cost of developing a medicine are typically higher for rare diseases, but the patient population that can benefit from the medicine are, by definition, smaller. This combination means that the
costs of medicines that treat rare diseases will be significantly higher than those of other medicines. As a result, relying on the typical cost-effectiveness thresholds of $50,000 to $175,000 is likely to be inappropriate for determining whether the new triple therapy medicine is cost effective.

Recognizing these concerns, ICER will, on a case-by-case basis, consider raising the cost-effectiveness threshold up to $500,000. With respect to this therapy, we recommend that ICER, at a bare minimum, apply this higher threshold

ICER Should Include Quantified Social and Economic Benefits into the Cost-Effectiveness Model

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 due to costs associated with hospitalization. While these are the average costs, 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.vi Younger patients diagnosed with severe cystic fibrosis incur even higher annual costs. Patients aged 10 to 14 with severe disease severity were estimated to be as high as $343,900.vii

These costs do not capture the full burden of the disease, the impact on caregivers, the lost economic opportunities, and the costs associated with patients’ shorter lifespan. To the extent that more effective treatment is able to reduce these costs, these benefits must be included in the quantitative cost-effectiveness models.

Conclusion

Not only is cystic fibrosis a devastating disease, most patients living with cystic fibrosis do not have access to an effective treatment. The results from clinical studies indicate that the addition of the new triple therapy will make treatment possible for around 90 percent of patients. The patient community is eager for this advance, and it is critical that ICER acknowledge that the value a broadly effective treatment creates for patients.

Due to the importance of this therapy to the patient community, IfPA urges ICER to account for the considerations outlined above when performing its clinical evidence review; otherwise, the review may provide an inaccurate picture of the benefits derived from adding the novel agent elexacaftor to the combination of tezacaftor and ivacaftor.

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


iv Joseph A (2019) “‘We’re still waiting’: As cystic fibrosis drugs deliver new hope, not everyone is being swept up by scientific progress” Stat News, February 4.


vii Ibid.