Introduction

CYSTIC FIBROSIS

Cystic fibrosis (CF) is a progressive genetic disease that affects many organ systems, though a significant proportion of its morbidity and mortality is associated with its respiratory impacts. In 2016, an estimated 30,000 individuals in the US were living with CF.

CF is linked to mutations in the CF transmembrane conductance regulator (CFTR) gene. While there are over 300 genetic mutations known to be associated with CF, the *F508del* mutation is most common, affecting 86% of patients. About half of those who have the *F508del* mutation have two copies of the mutation (homozygous), and the other half have one copy of *F508del* and a copy of another mutation (heterozygous). Other types of mutations include gating or residual function mutations such as *G551D* and *R117H*.

TREATMENT OPTIONS

ICER's report reviewed three CFTR modulator drugs:

- **Ivacaftor (Kalydeco®)** in people with gating and residual function mutations.
- **Lumacaftor/ivacaftor (Orkambi®)** in patients homozygous for the *F508del* mutation.
- **Tezacaftor/ivacaftor (Symdeko™)** in patients homozygous or heterozygous for the *F508del* mutation.

Given that the size of the patient populations eligible for treatment with the drugs under review in this assessment was approximately 10,000 individuals or fewer, ICER applied its framework for treatments of ultra-rare disorders.

Summary

ICER's report was reviewed at a public meeting of the Midwest CEPAC. A majority of the indepedent voting panel found that, in their specified indications, **Kalydeco, Orkambi, and Symdeko offer a net health benefit** compared to best supportive care alone, and provide other benefits such as reduced caregiver burden and new options for patients in whom other therapies have not been effective.

However, a majority of the Council voted that the therapies represent a low long-term value for money, due in large part to their high costs. ICER's analysis suggested that **discounts of up to 77%** would be necessary to bring the prices into alignment with the drugs' clinical value to people with CF and their families.

POLICY IMPLICATIONS

- The manufacturer bears a social responsibility to use restraint during its period of monopoly pricing power. Vertex should abandon claims that prices are justified by investments in future research and join the growing number of biotech innovators providing a transparent justification for prices based on treatments' abilities to improve the length and quality of patients' lives.
- Public and private payers should continue to affirm their commitment to providing access to important clinical advances for CF and remove superfluous requirements for coverage approval and continuation.
- Patient organizations with a leading role in funding, organizing, and promoting innovative research into new treatments should demand commitments from manufacturers for sustainable pricing of those products.

Clinical Analyses: ICER Evidence Ratings

How strong is the evidence that CFTR modulators improve outcomes in patients with CF?

The indicated therapies, used with best supportive care, were compared to best supportive care alone in each of the key populations.

Individuals with Gating and Residual Function Mutations	**Kalydeco**: High certainty of a substantial net health benefit
Individuals Homozygous for *F508del* Mutation	**Orkambi:** High certainty of a small net health benefit **Symdeko:** Moderate certainty of a small to substantial net health benefit, but high certainty of at least a small net health benefit
Individuals Heterozygous for *F508del* Mutation	**Symdeko**: Moderate certainty of a small or substantial net health benefit, but high certainty of at least a small net health benefit

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Key outcomes studied in trials included:

- Percent predicted forced expiratory volume in 1 second ($ppFEV_1$, a measure of lung function)
- Pulmonary exacerbations
- Weight and body mass index (BMI)
- Respiratory-related quality of life measured by the CFQ-R instrument.

Clinical Analyses: ICER Evidence Ratings (continued)

Individuals with Gating and Residual Function Mutations				
	Absolute ppFEV$_1$	**Pulmonary Exacerbation**	**Weight and BMI**	**Quality of Life**
Kalydeco	↑ Important improvement	↓ Large reduction (except in those with *R117H* mutation)	Mixed findings, depending on mutation	↑ Important improvement

Individuals Homozygous for *F508del* Mutation				
	Absolute ppFEV$_1$	**Pulmonary Exacerbation**	**Weight and BMI**	**Quality of Life**
Orkambi	↑ Modest improvement	↓ Large reduction	↑ Improvement in weight measures	↑ Small improvement
Symdeko	↑ Modest improvement	↓ Large reduction	No significant differences reported	↑ Important improvement

Individuals Heterozygous for *F508del* Mutation				
	ppFEV$_1$	**Pulmonary Exacerbation**	**Weight and BMI**	**Quality of Life**
Symdeko	↑ Important improvement	No significant differences reported; exploratory endpoints	No significant differences reported; exploratory endpoints	↑ Important improvement

HARMS

For each of the three CFTR modulators, harms were not serious and generally uncommon. Serious adverse events, as defined by the studies, commonly occurred at similar or *lower* rates among those taking the CFTR modulators than those taking placebos.

Reasons for CFTR modulator discontinuation included elevated liver enzymes, increased creatinine kinase levels, coughing blood, difficulty breathing, pulmonary exacerbation, and rash.

With Orkambi, about 10% to 20% of patients experienced chest tightness and 6% discontinued the drug due to adverse events. Chest tightness was uncommon with Kalydeco or Symdeko.

Clinical Analyses: ICER Evidence Ratings (continued)

SOURCES OF UNCERTAINTY

Generalizability of Trial Results: CF genetics are highly complex and variable, and the populations with any one type of mutation are relatively small. Furthermore, Symdeko's FDA approval was not limited to the population studied in trials, and it is unknown whether trial results expand to these populations.

Evidence Limitations: Many aspects of CF have not been systematically researched; thus, measures of the impact of CFTR modulators are highly dependent on those outcomes measured in the trial data. Important outcomes related to diabetes, nutrition, family and caregiver burden, and others have not been reported.

Key Outcome Measures: The degree to which reductions in pulmonary exacerbation rates are contingent on or independent from effects on lung function (measured by $ppFEV_1$) remains uncertain. Further, $ppFEV_1$ is a surrogate outcome, and it remains unclear what minimum magnitude of change is clinically relevant.

Long-term Effects: Data on the durability and nature of CFTR modulator effects on lung function are still emerging, particularly information on slowing of the rate of lung function decline over the longer term.

Access to Care: Many trials were conducted in accredited CF specialty centers. It is uncertain whether gains in survival are distributed unequally due to differences in access to CF care centers in the US.

Supportive Care: Best-practice symptom management for CF involves numerous therapies that positively impact pulmonary status, and many trial participants used CFTR modulators concurrently with other treatments. This may increase uncertainty around the incremental benefits of the CFTR modulators beyond those of best supportive care.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS AT LIST PRICE

Do CFTR modulators meet established thresholds for long-term cost-effectiveness?

ICER's economic analyses found that, in all populations considered, the cost of the drugs combined with best supportive care **far exceeded commonly accepted thresholds for cost-effectiveness of $100,000–$150,000 per quality-adjusted life year (QALY)** gained when compared to standard care.

ICER's report notes that decision-makers often give special considerations to therapies for ultra-rare diseases such as CF, which may lead to coverage and funding decisions at higher thresholds for cost-effectiveness.

Treatment vs. Best Supportive Care Alone	Cost Per QALY Gained
Individuals with Gating and Residual Function Mutations	
Kalydeco plus BSC	$956,800
Individuals Homozygous for *F508del* Mutation	
Orkambi plus BSC	$890,700
Symdeko plus BSC	$974,300
Individuals Heterozygous for *F508del* Mutation	
Kalydeco plus BSC	$941,100
Symdeko plus BSC	$840,600

Economic Analyses (continued)

ICER'S VALUE-BASED PRICE BENCHMARKS

What is a fair price for CFTR modulator therapies based on their value to patients and the health care system?

For each drug, the discounts required to align costs with benefits to patients are **much greater** than the currently assumed discount from wholesale acquisition cost (WAC).

	Annual WAC	Annual Net Price with Mark-up	Annual Price to Achieve $100,000–$150,000 per QALY	Discount from WAC to Reach Threshold Prices
Kalydeco	$312,000	$310,000	$73,000–$86,000	72%–77%
Orkambi	$273,000	$264,000	$68,000–$80,000	71%–75%
Symdeko	$292,000	$283,000	$68,000–$81,000	72%–77%

**Includes mark-up typical of hospital-administered drugs*

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated with Symdeko before crossing ICER's $915 million budget impact threshold?*

Potential budget impact was estimated for Symdeko in those heterozygous or homozygous for the *F508del* mutation. The annual potential budgetary impact of treating the combined eligible populations with Symdeko at the net price over five years reached 95% of the $915 million threshold. At WAC price, costs exceeded the threshold by 2%.

Treatment for patients homozygous for the *F508del* mutation reached 60% of the budget impact threshold; treating patients heterozygous for the *F508del* mutation reached 34% of the threshold.

**Budget impact for the other therapies was not calculated given their established presence on the market.*

Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on May 17, 2018. More detail on the voting results is provided in the full report.

A majority of the Council voted that, in their specified indications, Kalydeco, Orkambi, and Symdeko in combination with best supportive care all offer a net health benefit compared to best supportive care alone.

Many members of the Midwest CEPAC noted that the therapies offer other benefits beyond those looked at in clinical trials, such as reduced caregiver burden, a treatment option for patients in whom other therapies have not been effective, and improved ability for patients to return to work, school, or other activities. Council members further voted that contextual considerations, such as the high severity of disease with a high lifetime burden of illness, must also be considered in determining the long-term value for money of the therapies.

Despite these positive findings, however, a majority of the Council ultimately voted that the therapies represent a low long-term value for money, due in large part to the high price of the drugs.

Key Policy Implications

The Midwest CEPAC participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the full report.

PRICING AND ACCESS

The prices for CFTR modulators are too high, harming patients and families today while threatening the health care system's ability to maintain access for all patients to important future clinical advances. Benefiting from monopoly pricing power, the company bears a significant social responsibility to change its pricing approach by committing to the following two actions:

- Abandon vague claims that prices are justified by the need to invest in future research and instead join the growing number of biotech innovators who provide a transparent, explicit justification for their prices based on the ability of treatments to improve the length and quality of patients' lives;
- Accept that the process for determining a reasonable price for new drugs requires innovators, especially those with monopoly pricing power at their disposal, to exercise restraint and be open to an independent process to evaluate fair pricing that includes the full engagement of the innovator, patients, patient advocacy groups, clinical experts, insurers, and other stakeholders.

- Public and private payers should continue to affirm their commitment to provide access to important clinical advances for CF and should remove superfluous requirements for coverage approval and continuation.
- Since insurance coverage denial for CF drugs is off the table, payers should be willing to develop and adopt new approaches to moderate the impact of monopolistic pricing power. One example of a possible approach is the recent program implemented by the New York Medicaid program to highlight medications that contribute to growth in pharmaceutical spending above a designated budget cap.
- Patient organizations that have a leading role in funding, organizing, and promoting innovative research on new treatments should demand commitments from manufacturers for sustainable pricing of the products patients helped bring to the market.
- Professional societies should highlight the impact on their patients of failed pricing and insurance policies and demand to be part of the public process that should guide pricing to balance the needs for affordability and for investments in future innovation.

FUTURE RESEARCH

- Future studies should measure and report a broad set of outcomes to better assess the health and economic impact of CF interventions to patients, their caregivers, and their health system.
- Manufacturer-sponsored research should enroll patients who are often encountered in clinical practice, but who are routinely excluded from clinical trials.
- Leverage all available resources to maximize the evidence base.

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-review.org).