REPORT AT A GLANCE: CHRONIC OBSTRUCTIVE PULMONARY DISEASE

JULY 2024

KEY FINDINGS

Population	Treatment	Comparator	Evidence Rating	Annual WAC	Health-Benefit Price Benchmark
Moderate-to-severe COPD	Ensifentrine	Maintenance therapy alone	B+	$35,400	$7,500 to $12,700

"COPD is a common cause of severe respiratory problems. Current evidence shows that ensifentrine decreases COPD exacerbations when used in combination with some current inhaled therapies, but there are uncertainties about how much benefit it may add to unstudied combinations of inhaled treatments. Unfortunately, the manufacturer chose a price for ensifentrine far above the value-based price. This may lead payers to implement formulary hurdles that could limit provider and patient access to this promising new treatment."

– ICER's Chief Medical Officer David Rind, MD

THEMES AND RECOMMENDATIONS

- All stakeholders have an important role to play in ensuring that effective treatment options for COPD are implemented in a manner to reduce health inequities. For example, manufacturers should set up broad distribution networks, payers should cover all effective smoking cessation therapies, and all stakeholders should advocate for better access to all effective therapies for COPD, including drugs, supplemental oxygen, and pulmonary rehabilitation.
- By setting the price of ensifentrine far above commonly used cost-effectiveness thresholds, the manufacturer has missed an opportunity to provide broad access and increased uptake of the drug.
- Since COPD is both over and underdiagnosed, there is a role for all stakeholders to improve the infrastructure for diagnosis. This includes increasing access to spirometry (including new paradigms of care), ensuring adequate reimbursement for spirometry, and developing and implementing new biomarkers for the diagnosis of COPD.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases characterized by progressive and persistent airflow obstruction in the lungs. The most common forms of COPD are emphysema and chronic bronchitis; cigarette smoking, including secondhand smoke, is the leading cause of COPD in the United States (US). COPD affects nearly 16 million people in the US, is the 6th leading cause of death, results in more than one million emergency department visits and 500,000 hospitalizations, and results in costs of almost $50 billion per year.

Symptoms of COPD include persistent shortness of breath, fatigue, wheezing, chest tightness, sputum production, and cough. Symptom burden is high, with more than 50% of people living with COPD experiencing daily symptoms, particularly shortness of breath and fatigue, which can limit activities. In people with more severe disease, reliance on caregivers for many routine independent activities of daily living (e.g., dishwashing, laundry) is common. Although inhaled therapy can be effective, currently available medications do not necessarily address all COPD symptoms, and side effects can be burdensome for some. Oxygen therapy may be required for people with severe COPD and may limit mobility outside of the home due to the weight of the oxygen tanks or the limited battery life of a portable oxygen concentrator.

Treatment of COPD includes non-pharmacologic measures such as smoking cessation, vaccinations, and pulmonary rehabilitation, as well as pharmacologic therapy. The goals of pharmacologic therapy are to improve symptoms and reduce exacerbations. The mainstay of therapy is inhaled bronchodilators, including long-acting beta-2-agonists (LABA) and antimuscarinics (LAMA) to relieve symptoms, improve lung function, and reduce exacerbations. Combination therapy with LAMA + LABA therapy, when indicated, is more effective than monotherapy. The addition of inhaled corticosteroids (ICS) can be considered for patients with frequent exacerbations and a blood eosinophil count of ≥ 300 cells/µl. For patients with frequent exacerbations, additional treatment options such as roflumilast, azithromycin, or N-acetylcysteine may be added. For patients with severe or very severe disease, long-term, continuous supplemental oxygen may be needed; lung volume reduction surgery may be considered in certain cases.

Despite therapy, nearly two-thirds of patients report continuing to have symptoms of COPD. Ensifentrine (Ohtuvayre, Verona Pharma) is a novel inhaled dual inhibitor of PDE3 and PDE4 enzymes that relaxes airway smooth muscle and decreases inflammation. It was approved by the US Food and Drug Administration (FDA) on June 26,2024 as an add-on maintenance treatment of moderate to severe COPD. It is delivered twice daily via standard jet nebulizer. Ensifentrine was evaluated in two 24-week multicenter, randomized, placebo-controlled trials (ENHANCE-1 and -2), with ENHANCE-1 including an additional 24 week safety extension. Participants had moderate to severe COPD and were on stable background therapy, including no therapy or LAMA or LABA, with or without ICS. Patients on dual LAMA+LABA therapy or triple LAMA+LABA+ICS were excluded from the trials. Participants in the trials had a mean age of around 65 years and were mainly white; 50-60% had moderate disease, 20-25% had an exacerbation within the last 15 months, and 30-45% were on no background therapy at baseline.

Treatment with ensifentrine met the primary endpoint of the trials of improving measures of lung function, including average FEV_1, at 12 weeks. It also

Clinical Analyses

decreased the annualized rate of moderate to severe exacerbations by 40%, with a pooled rate ratio of 0.60 (95% confidence interval [CI] 0.41, 0.79) at week 24. Time to first exacerbation was also delayed by 40% at week 24, a benefit that was maintained in the safety extension of ENHANCE-1. Ensifentrine had mixed impact on quality of life measures with statistically significant improvements in some measures but not in others or in only one of the two trials. Ensifentrine was well-tolerated with similar rates of adverse events and discontinuation in the ensifentrine and placebo arms.

The trials were conducted during the COVID-19 pandemic, leading to multiple trial withdrawals either from COVID infection or, presumably, because of patient concerns about trial participation during the pandemic. These withdrawals increase uncertainty and could potentially bias results. The exclusion of patients on LAMA + LABA or triple therapy raises questions about the benefits of ensifentrine when added on to recommended regimens.

While the results of ENHANCE-1 and -2 are promising, there remains some uncertainty about the magnitude of overall benefit in patients receiving the most optimized modern inhaler therapies for COPD, although there was no effect modification by background therapy type in the trials. We do not have significant concerns about harms with ensifentrine. For these reasons, we have high certainty that ensifentrine added to maintenance therapy, compared with maintenance therapy alone, results in at least a small net health benefit, and may result in substantial net health benefit ("B+"). We have somewhat greater certainty in the benefits when ensifentrine is added to the regimens studied than to regimens that combine LABA and LAMA therapy.

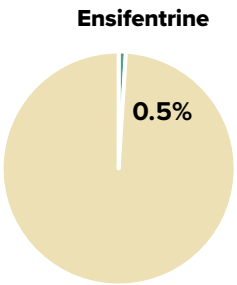
Economic Analyses

LONG-TERM COST EFFECTIVENESS

In cost-effectiveness analyses, ensifentrine results in fewer exacerbations and in greater QALYs, evLYs, and life years. At a wholesale acquisition cost of $35,400 per year, the incremental cost-effectiveness ratios for ensifentrine are $492,000 per QALY gained and $426,000 per evLY gained. Ensifentrine would meet commonly used cost-effectiveness thresholds at an annual price between $7,500 and $12,700. If ensifentrine is shown to increase the day-to-day quality of life of patients living with COPD, beyond quality of life improvements associated with fewer exacerbations, the cost-effectiveness would improve, but would continue to exceed commonly used cost-effectiveness thresholds at an annual price of $35,400.

POTENTIAL BUDGET IMPACT

At the price of $35,400 per year for ensifentrine, approximately 0.5% of US patients eligible could be treated within five years without crossing the ICER potential budget impact threshold of $735 million per year.



Percent of eligible patients with COPD that could be treated in a given year before crossing the ICER potential budget impact threshold

Economic Analyses

ICER is issuing an access and affordability alert for ensifentrine for the management of COPD. The purpose of an ICER access and affordability alert is to signal to stakeholders and policymakers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services, creating pressure on payers to sharply restrict access, or causing rapid growth in health care insurance costs that would threaten sustainable access to high-value care for all patients.

Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted on, the evidence of ensifentrine for adults with moderate-to-severe COPD:

- A majority of panelists (11-4) found that current evidence is **adequate** to demonstrate a net health benefit for ensifentrine added to maintenance therapy when compared to maintenance therapy alone.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.
- This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.

Consistent with ICER's process, because there was no firm estimate yet of a potential launch price for the treatment at the time of the public meeting, the panel did not take a vote on the treatment's long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.