Ensifentrine for the Maintenance of Chronic Obstructive Pulmonary Disease

Draft Background and Scope

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Background

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases characterized by progressive and persistent airflow obstruction in the lungs. COPD affects approximately 15.7 million people in the United States, with higher rates among non-Hispanic White individuals, Native American individuals, women, and adults older than 65.[1] It is the 6th leading cause of death among Americans[2] and is the cause of over 500,000 hospitalizations, one million emergency department visits per year, and 16.4 million lost working days per year.[3,4] The total economic burden of COPD is estimated to be almost $50 billion per year, with $29.5 billion attributable to direct medical costs.[3]

The two most common forms of COPD are chronic bronchitis and emphysema. While chronic bronchitis is characterized by airway inflammation that causes mucus production, the hallmark of emphysema is destruction of alveoli causing difficulty with oxygen exchange. Both forms of the disease cause shortness of breath, fatigue, wheezing, chest tightness, and cough, and they often coexist. In very severe COPD, patients may lose weight, have anorexia, or develop right-sided heart failure. The leading causes of COPD in the United States (US) are cigarette smoking, including exposure to secondhand smoke, and exposure to airborne irritants and pollutants.[5] Workplace exposures such as dust, fumes, gases, chemicals are the most common causes of COPD among non-smokers.[6] Other causes include pre-existing lung injury (e.g., prematurity, prior infections) and alpha-1-antitrypsin deficiency.[5] Women with COPD have been observed to be younger, smoke less, and have more dypsnea than men;[7] women also account for a higher proportion of hospitalizations.[8] Lower socioeconomic status has been linked with greater disease progression.[9] Finally, chronic bronchitis may be associated with worse clinical outcomes, including worse symptoms, quality of life, and lung function, and more frequent exacerbations.[10]

Diagnosis of COPD is based on symptoms and evidence of airflow obstruction, defined as a post-bronchodilator forced expiratory volume/forced vital capacity ratio (FEV1/FVC) of <0.7.[11] However, since symptoms and exacerbations may not necessarily correlate only with the degree of airflow obstruction, treatment of COPD is based on a combined assessment of the severity of airflow limitation, exacerbation history, and symptom status. In those patients who smoke, smoking

cessation is a key component of treatment. Other non-pharmacologic therapies such as pulmonary rehabilitation, can also improve exercise capacity, symptoms, and quality of life; vaccinations can decrease the incidence of lower respiratory infections.

The goals of pharmacologic therapy in COPD are to reduce symptoms and risk of exacerbations. The mainstays of pharmacologic therapy are inhaled bronchodilators, including beta-2-agonists and antimuscarinic drugs, which improve airflow by relaxing airway smooth muscle tone.[11] While short-acting beta-2-agonists (SABA) and antimuscarinics (SAMA) are helpful for relieving symptoms, long-acting beta-2-agonists (LABA) and antimuscarinics (LAMA) can improve lung function, dyspnea, health status, and reduce exacerbations. Furthermore, combination therapy with LABA + LAMA therapy is more effective than monotherapy.[12] For patients with moderate to very severe COPD, particularly those with a hospitalization for COPD exacerbation, ≥2 moderate exacerbations per year, or a blood eosinophil count ≥300 microliter, inhaled corticosteroids (ICS) in addition to LABA + LAMA is more effective than monotherapy in improving lung function and reducing exacerbations and may reduce mortality.[13] However, long-term use of ICS may increase risk of pneumonia.[14] For very severe COPD, there may be a role for the phosphodiesterase-4 (PDE-4) inhibitor roflumilast, long-term continuous oxygen therapy, which has been shown to decrease mortality[15], or lung volume reduction surgery.[11]

Ensifentrine (Verona Pharma) is a novel inhaled dual inhibitor of PDE3 and PDE4 enzymes for maintenance treatment of COPD. Inhibition of PDE3 and PDE4 enzymes can relax airway smooth muscle, decrease inflammatory cells, and improve ciliary function.[16] The drug is delivered twice-daily via nebulizer. The manufacturer has submitted a new drug application with the US Food and Drug Administration (FDA) for ensifentrine for maintenance treatment of COPD, with a decision expected by June 26, 2024.[17]

Stakeholder Input

ICER scoping documents are developed with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders, review of publicly available statements from patients and patient organizations, and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Individuals living with COPD describe limitations in their daily activities, often due to shortness of breath and fatigue. For example, patients describe the requirement for more energy than usual to complete tasks. Since symptoms can vary from day to day, there is a need to plan ahead and for patients to pace themselves – e.g., learning to sit and rest between activities, not going out when

it's too hot or humid, and learning proper breathing techniques to help with shortness of breath. Pulmonary rehabilitation and regular exercise also play important roles in helping individuals with COPD maintain quality of life. With more severe disease, shower chairs, bedside commodes, and/or wheelchairs may be helpful.

Prevention of exacerbations is an important part of disease management. Patients describe trying to avoid respiratory infections as much as possible with strategies such as avoiding large group gatherings and wearing masks when going out of the house. Avoidance of respiratory irritants such as secondhand smoke, diesel fumes, chemical fumes, and smoke from wood-burning stoves and fireplaces is also important. Some patients and clinicians form a written plan to help patients understand what their respiratory status is and potential interventions when they are having increased symptoms (e.g., American Lung Association COPD Action Plan).

Caregiving for COPD involves helping patients primarily with symptom and medication management for patients with less severe disease. This is particularly relevant for older patients and those with comorbidities, as they may have additional challenges with medication adherence. In particular, such patients may not have the coordination required for correct inhaler usage or may require careful monitoring or adaptations to treatment due to the possibility that the effects of COPD medications may exacerbate other conditions.[18,19] As the disease progresses, caregivers may need to take on more physical chores such as shopping, cooking, housekeeping, and hygiene needs. Anxiety and depression are more common in individuals with COPD, and caregivers may need to help patients with emotional and psychological support.

Report Aim

This project will evaluate the health and economic outcomes of encifentrine for COPD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers,

and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with moderate to severe chronic obstructive pulmonary disease (COPD).

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Sociodemographic factors (e.g., sex, age [e.g., >75 years], socioeconomic status)
- Medical comorbidities (e.g., hypertension, osteoporosis, obesity)
- Eosinophil count (>300 or <100 cells/µl)
- People with frequent exacerbations (e.g., ≥2 moderate exacerbations per year or ≥1 leading to hospitalization per year)
- Emphysema versus chronic bronchitis
- Moderate versus severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] classification 2 versus 3)

Interventions

The intervention of interest for this review is:

- Ensifentrine (Verona Pharma)

Comparators

We intend to examine ensifentrine as an add on therapy to current COPD maintenance therapy versus no additional treatment.

- Current maintenance drug therapies include:
    - Long-acting beta-agonists (LABAs)
    - LABA and inhaled corticosteroids (ICS)
    - Long-acting muscarinic antagonists (LAMAs)
    - LAMA and ICS
    - LABA and LAMA
    - Triple therapy: LABA, LAMA, and ICS

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Changes in dyspnea (e.g., transitional dyspnea index [TDI])
    - COPD-related hospitalization or emergency room visit
    - Use of rescue medication
    - Requirement for long-term continuous or intermittent oxygen use
    - Quality of life (e.g., St. George's Respiratory Questionnaire [SGRQ])
    - Number of exacerbations
- Changes in lung function (e.g., changes in average or peak forced expiratory volume [FEV_1])
    - Change in GOLD category
- Adverse events (AEs) including but not limited to:
    - Serious AEs
    - Discontinuation due to AEs
    - Other AEs including but not limited to:
        - Mortality
        - Pneumonia
        - Cardiovascular outcomes (e.g., myocardial infarction, ischemic heart disease, stroke, hypertension)
        - Urinary tract risks

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities*
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.
The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.
The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of ensifentrine added on to current maintenance therapy relative to current maintenance therapy alone. Within this scoping document, we describe the model population, intervention, comparator, outcomes of interest, time horizon, and a potential model structure based on current understanding of the topic. A detailed economic model analysis plan with proposed methodology, detailed model structure, model parameters, model inputs, and model assumptions will be forthcoming.

The model structure will be based in part on a literature review of prior published models of COPD.[20-22] Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Patient and caregiver productivity impacts and other indirect costs

will be considered in a separate modified societal perspective analysis. The modified societal perspective analysis will be considered as a co-base case when direct data on indirect costs are available, the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

The target population will consist of adults with moderate to severe COPD. The model will consist of health states defined by the GOLD disease severity classification and death. Each of the disease severity health states will have associated health states for stable disease, non-severe exacerbation, and severe exacerbation. A cohort of patients will transition between the health states during predetermined cycles of three months over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated from the randomized controlled trials and may include effects on lung function and exacerbations.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of exacerbations avoided, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life year gained, and cost per exacerbation avoided.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by ensifentrine (e.g., reduced need for emergency department visits and hospitalizations), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of COPD beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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