May 7, 2024

Sarah K. Emond, MPP
President and Chief Executive Officer
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

RE: Comments on Draft Evidence Report on Ensifentrine for the Treatment of Chronic Obstructive Pulmonary Disease

Dear Ms. Emond:

The COPD Foundation (Foundation) appreciates the opportunity to comment on the Draft Evidence Report (Report) by the Institute for Clinical and Economic Review (ICER) for its assessment of Ensifentrine for the treatment of COPD. The Foundation's mission is to help millions of people live longer and healthier lives by advancing research, advocacy, and awareness to stop COPD, bronchiectasis, and NTM lung disease.

It is important to frame these comments in the larger context of the significant burden, unmet medical need, and correspondingly urgent demand for more effective treatment facing people with COPD and their care partners. The Foundation is investing in research, regulatory, and access strategies to this end and encourages ICER to recognize these realities as the assessment process unfolds. Specific considerations include:

- Focusing additional research resources and various treatment development tools on the earliest stages of the disease to fundamentally alter or arrest its progression.
- Aligning the measures of clinical effectiveness for emerging therapies on the areas demonstrated to be of greatest importance to people living with COPD.
- Recognizing that factors other than tobacco use are increasingly contributing to the societal burden of COPD.
- Ensuring disproportionate impact of COPD on underserved populations, including in rural areas, is central to improving treatment outcomes.

This review creates assumptions for COPD treatment value assessments that will likely endure. Therefore, it is critical for ICER to recognize current treatment practices and include all relevant outcomes. As ICER conducts its assessment of treatments for COPD, we urge you to consider the following comments.

1. **Using outdated approaches as the foundation of the model hinders this review and sets a dangerous precedent for future assessments of new COPD treatments.**
   The current model structure uses a dated approach to COPD severity classification based solely on lung function. Current GOLD guidance uses symptoms and exacerbations (moderate and severe) to classify a patient's severity for guiding therapy.[1] We again

encourage ICER to update the analysis approach to better represent current guidance to classify COPD severity important for treatment decisions.

2. **ICER should update the model structure to include all possible health states.**
In the current GOLD guidance paradigm, patients can become worse or better (if exacerbations and/or other symptoms decrease).[1] The model only allows staying in the same health state or worsening. Allowing for a change to a less severe health state with treatment could be a key benefit of new treatments for COPD. Model structures described in similar assessments have previously allowed patients to transition to less severe health states.[2]

3. **Capturing all aspects of lived experience is critical when quantifying disease impacts and treatment potential.**
The current model includes treatment benefits centered around exacerbation. While exacerbations are important, these events do not represent the everyday impacts of those living with COPD. Treatment effects that matter most to patients include the relief for daily symptoms of breathlessness, cough and sputum, and fatigue.[3] The current model approach should include treatment effects on daily symptoms and associated impacts on health-related quality of life (HRQoL) that are reported in the ENHANCE 1 and 2 trial results.

   The importance of inclusion of HRQoL is confirmed in the Report, where ICER notes that cost-effectiveness would improve if HRQoL results were included independent of exacerbations. Instead, ICER assumed that the full effect of treatment on HRQoL should be attributed to exacerbation events only. The rationale for this assumption is unclear when considering the specific patient reported outcome (PRO) assessments included in the trials for several reasons:

   - The recall period of relevant PROs is limited to either "now/today" or over a short timeframe prior to a study visit.
   - Based on the frequency of exacerbations, most patients would not have experienced an exacerbation when they completed the PROs at study visits. Therefore, most of the responses for relevant HRQoL PROs would not be influenced by an ongoing or recent exacerbation.
   - PRO results were directionally consistent across a variety of symptom and impact measures.
   - Inclusion of the EQ-5D-5L in the ENHANCE 2 trial provides a simple way to incorporate HRQoL impacts in the model beyond exacerbations. As noted in the Report, in ENHANCE 2, a statistically significant increase in EQ-5D-5L at week 24 was observed compared to placebo (MD versus placebo: 0.027; 95% CI: 0.004, 0.050; P=0.019). By this timepoint (i.e., week 24) most of the patients had not experienced an exacerbation providing confidence that these results represent everyday experience with COPD.

   Based on the frequency of exacerbations, the timing of the PRO responses, and the PRO recall periods, ICER should incorporate HRQoL impacts independent of exacerbation into this model to better represent all patient important impacts of treatment.

4. **ICER should reconsider the data source for healthcare costs to ensure the current experience of COPD patients in the United States is accurately represented.**
   Healthcare costs for exacerbations were estimated based on analysis from a clinical trial.[4] Estimating healthcare resource use (HRU) and associated costs from clinical trial populations is not representative of the overall population and typically underestimates HRU and cost. An alternative source for this input should be used to represent costs of COPD.[5]

5. **ICER should acknowledge the limitations of the current analysis approach in fully representing the full impact of COPD on patients and caregivers.**
   The current analysis approach does not include other important impacts of COPD due to limited available evidence. The current modified societal perspective does consider patient and caregiver productivity and unpaid caregiver time. Data on other indirect impacts such as, caregiver health and quality of life, patient and caregiver out-of-pocket costs, or other support services, were not available for inclusion. ICER should clearly note in the Report the limited inclusion of broader impacts of COPD.

6. **ICER should include additional comparator groups as part of the base-case analysis to better represent the trial population and current treatment recommendations.**
   The current model assumes ensifentrine will be used as an add-on therapy for all patients (currently treated with mono, dual or triple therapy), although clinical trials for ensifentrine included adults with COPD of all levels of severity, including people on no maintenance therapy. Additionally, no more that 50% of patients were allowed on either LAMA or LABA maintenance therapy at inclusion. At model entry, the cohort should include an option to better mirror the trial population, with patients transitioning to alternative maintenance treatment basket options in later cycles of the model.

   Scenarios that include additional comparisons or treatment options across cycles would be more aligned with the current treatment approaches (e.g., LABA + LAMA versus LABA + ensifentrine, or LABA+LAMA+ICS versus LABA+LAMA+ensifentrine). Altering the approach could show more cost-effective scenarios and improve the utility of the overall analysis and Report.

   Updating the model treatment approach to allow for treatment discontinuation and changes also provides the opportunity to align with impacts of longer-term adverse events associated with current treatments, such as infections and cardiovascular disease, and better represents the current recommendations for COPD Action Plans to be updated every six months.[6]

7. **Additional causes of discontinuation should be included in the model to accurately represent treatment duration.**
   It seems unrealistic that discontinuation is only driven by adverse events at week 12 in a life-time model. In most models, there is a waning effect or a move to later lines of therapy. ICER should account for other causes of discontinuation and discontinuations after week 12.

8. **Clarify how the model applies disutilities for exacerbations.**
   Additional detail is needed in the Report to clarify if the decrement is applied for the entire one-year cycle length and how more than one exacerbation during the cycle is handled. Note,

other models use 1-month cycles which allow for a more granular assessment of exacerbation impact and capture these disutilities more intuitively.

9. **Clarify how productivity costs are scaled to reflect the proportion of patients/caregivers who are likely retired or non-working.**
   The current Report is unclear how productivity costs are applied at a population level. ICER should clarify if the proportion of non-working is accounted for in the model calculations for productivity.

10. **Additional detail should be included to clarify specific healthcare costs included in the assumptions.**
    While the healthcare total cost inputs may be appropriate, ICER should note what costs are specifically included in assumptions/inputs for full transparency and so others can determine if potential costs are missing from the inputs (e.g., primary or specialist care, rescue medications, device costs, oxygen).

We appreciate your consideration of these comments.

Sincerely,

Jean Wright, MD, MBA
Chief Executive Officer
COPD Foundation

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[3] "Guides for Better Living" The COPD Foundation, www.copdfoundation.org/Learn-More/Educational-Materials-Resources/Downloads.aspx#guides
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GLOBAL ALLERGY & AIRWAYS
PATIENT PLATFORM

May 7, 2024

Institute for Clinical and Economic Review (ICER)
14 Beacon St, Suite 800
Boston, MA 02108

RE: GAAPP response to the draft evidence report for ICER's value assessment of ensifentrine for COPD

Dear ICER Review Team:

On behalf of the Global Allergy & Airways Patient Platform (GAAPP), thank you for the opportunity to provide comments regarding ICER's *Draft Evidence Report on Ensifentrine for Chronic Obstructive Pulmonary Disease (COPD)*.

About GAAPP

GAAPP is a non-profit organization dedicated to raising global standards for the treatment, diagnosis, and care of patients with allergies, airways, and atopic diseases. It supports member organizations worldwide to address the unmet needs of their local patient communities. GAAPP operates on the pillars of awareness, education, advocacy, and research, aiming to empower patients and improve their quality of life. The platform collaborates with healthcare and governmental organizations to drive policy changes, improve care quality, and facilitate global communication among patient groups.

Draft Evidence Report Comments

As ICER finalizes its evidence report, GAAPP urges you to consider the ongoing challenges and significant toll that COPD continues to take on patients, their families, and the healthcare system.

COPD Continues to Exact a High Clinical Burden

COPD is not just a medical condition – it is a pervasive crisis that represents the third leading cause of death globally.[i] COPD-associated deaths have increased by 30% worldwide between 1990 and 2010, further underscoring the fatality of the disease.[ii]

The symptom burden associated with COPD is significant, especially dyspnea, or shortness of breath, which remains the most bothersome symptom that patients note experiencing. Dyspnea and other symptoms are also associated with an increased risk of exacerbations.[iii] The health risks associated with exacerbations are acute, with patients facing an almost fourfold increase in the risk of cardiovascular events, such as heart attacks, within 30 days post-exacerbation.[iv] Experiencing two or more moderate exacerbations can increase a patient's risk of a future severe exacerbation by 61%.[v] The healthcare resource use associated with these exacerbations is significant, with up to 20% of patients requiring at least one hospital admission per year.[vi] COPD-related hospitalizations are also associated with an increased mortality risk, especially in the period post-admission, where mortality has been observed to increase by 43% two years post-discharge.[vi]

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Quantifying the Impact of COPD on Patient Quality of Life Remains Difficult

While COPD-specific quality of life instruments exist – such as St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C), the COPD Assessment Test (CAT), and the Clinical COPD Questionnaire (CCQ) – these tools are designed to help clinicians assess patients' health status and tend to focus on physical symptoms and limitations. They do not fully address the psychosocial aspects of COPD that affect a patient's ability to engage in meaningful activities such as remaining employed, playing with grandchildren, traveling, or participating in community events.

COPD Imposes a High Burden on the Health System Due to Direct and Indirect Costs

The economic impact associated with COPD is expected to rise to $4.8 trillion globally by 2030, reflecting the extensive resources required to manage this disease.[vii] In many countries, including the United Kingdom (UK) and Canada, COPD is the second most common cause of emergency admissions.[viii,ix] This high rate of hospitalization places a significant strain on healthcare systems, with nearly 50% of COPD costs in Europe attributed to these hospital stays.[x] Among patients who are employed, COPD leads to substantial income losses, with a survey across six countries estimating an average loss of $7,365 due to missed work.[xi] Moreover, approximately 40% of patients are forced into premature retirement due to COPD, resulting in lifetime income losses of $316,000.[xi]

Conclusion

There continues to be a high unmet need for patients with COPD. It is imperative during value assessments of new innovations that we acknowledge the full spectrum of its impact – from the direct costs of medical care to the indirect costs borne by patients and their families. As we consider future healthcare policy and resource allocation in COPD, access to a new drug class with a novel mechanism of action will provide hope and increased health for patients whose COPD is not adequately managed with the current drug classes available. As a global advocacy community, we urge ICER to consider the broader scope of physical, mental, psychosocial & financial impact to the COPD patient and carer community and society.

Sincerely,

Tonya A. Winders

Tonya Winders
President, GAAPP

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May 6, 2024

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RE: Draft evidence report for assessment of ensifentrine for the treatment of chronic obstructive pulmonary disease (COPD)

Dear Ms. Emond,

GSK appreciates the opportunity to provide comments in response to the draft evidence report for ICER's assessment of ensifentrine for COPD. With over 50 years of experience in respiratory care, GSK is committed to helping patients breathe better by continuously redefining treatment for COPD. While no GSK therapies are interventions of interest in this assessment, given our experience in COPD, we offer the following suggestions on the draft evidence report for ICER's consideration.

As outlined in our previous letter in response to ICER's draft scoping document, we believe it is inappropriate to include LAMA/LABAs and triple therapies (ICS/LABA/LAMA) in the comparator basket of maintenance therapies given that patients using these therapies were excluded from the ENHANCE trials of ensifentrine.[1] Throughout the assessment, ICER applies data focused on a limited set of maintenance therapies to a broad set of available therapies, when there are significant differences in guideline recommendations, patient characteristics, disease severity, and outcomes across these therapies.[2]

In the draft evidence report, ICER acknowledges that triple therapy "has become standard of care in symptomatic patients and/or those with frequent exacerbations." ICER references evidence from an observational study of a different add-on product, roflumilast, to justify the inclusion of triple therapies in the comparator basket, but then goes on to note that the exclusion of triple therapies from the ENHANCE trials, along with LAMA/LABA therapies, "raises questions about the benefits of ensifentrine when added on to some of the most recommended regimens." Nonetheless, ICER concludes there is "high certainty that ensifentrine added to maintenance therapy, compared with maintenance therapy alone, results in at least a small net health benefit." We find it challenging to reconcile these two statements, and question ICER's "high certainty" in its conclusion of added

[1] Notably, the exclusion of LAMA/LABA and triple therapies from the ENHANCE trials may have labeling implications.
[2] Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management, And Prevention, 2023 Edition. Available at https://goldcopd.org/wp-content/uploads/2023/03/POCKET-GUIDE-GOLD-2023-ver-1.2-17Feb2023_WMV.pdf.

benefit to the full set of maintenance therapies included in the comparator basket – especially LAMA/LABA and triple therapy.

The inclusion of LABA/LAMA and triple therapies in the comparator group of maintenance therapies also results in questionable results in the cost-effectiveness analysis. ICER applies an exacerbation rate ratio taken from pooled data from the ENHANCE trials and applies it to all maintenance therapies, despite the fact that LAMA/LABA and triple therapies were excluded. There is no scientific basis for assuming that exacerbation rate ratio applies to LAMA/LABA and triple therapies, which have demonstrated a more significant impact on exacerbation rates than other maintenance therapies.[3,4] The exacerbation rate ratio is by far the most significant factor in the results of the cost-effectiveness analysis, as shown in the tornado diagram (Figure 4.2); the relative impact of this input and the lack of direct evidence supporting its application to some of the most widely used therapies creates significant uncertainty in the results of the cost-effectiveness analysis.

Finally, in the cost-effectiveness analysis ICER uses data from a 2011 systematic review[5] as the model inputs for baseline exacerbation rates. Data from the studies included in the systematic review were largely from placebo and "minimal treatment" arms in various trials that pre-date the introduction of modern COPD therapies that have demonstrated greater effectiveness in reducing exacerbations. Thus, baseline exacerbation rates in the current general population of COPD patients on maintenance therapy are unlikely to match the rates included as model inputs. This results in additional uncertainty in the cost-effectiveness model results, especially as applied to newer regimens like triple therapies.

In conclusion, we can understand the decision to pool together maintenance therapies into one general comparator, given that ensifentrine is an add-on therapy. However, we are concerned that conclusions will be drawn regarding the additional benefit and value of ensifentrine added on to LAMA/LABA and triple therapies that have little clinical or scientific basis. At a minimum, we suggest that ICER reconsider the level of confidence in its results.

Thank you again for the opportunity to comment on the draft evidence report. If you have any questions about our comments, please contact Russ Montgomery at russ.w.montgomery@gsk.com.

Sincerely,

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PIPC Partnership to Improve Patient Care

May 7, 2024

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Dear Ms. Emond,

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) assessment on chronic obstructive pulmonary disease (COPD).

COPD impacts almost 16 million Americans. It is a highly heterogeneous condition, which can make it challenging to treat.[1] Given this reality, it is important that ICER accurately capture the value of new treatments, as segments of the patient population still desperately need new options. We encourage ICER to consider the following comments.

ICER's sources of data do not accurately capture the reality for COPD patients in the United States.

ICER's choice of data for costs per exacerbation appear to underestimate the true cost of exacerbations in the United States. The ICER model uses a single study that found the cost of moderate exacerbation estimated at $2,415 and a severe exacerbation at $26,047. This study relies on a sample of 300,000 patients. A much larger recent study that utilized data from CMS[2] suggested a range of cost per exacerbation of between $26,544 - $43,774 based on category of severity. This data relied on a much larger sample size of just under four million patients. In this instance, the more recent study with a larger sample population appears to provide more credible data. We would suggest that, where available, ICER should be using the most recent and largest studies.

We are also concerned that the sources used for mortality modifiers by COPD severity may underestimate the years of life lost due to COPD. The ICER model assumes standardized mortality ratios compared to those without COPD as 1.3 for moderate, 1.6 for severe and 1.9 for very severe.[3] The original source is a European study using Eurostat data from 21 countries, and states that the measures of severity varied widely by country. The paper itself is a request to improve standardization of outcome measures in COPD. There is a better source for mortality

[1] https://www.copdfoundation.org/What-is-COPD/Understanding-COPD/What-is-COPD.aspx
[2] Sethi S, Make BJ, Robinson SB, Kumar S, Pollack M, Moretz C, Dreyfus J, Xi A, Powell D, Feigler N. Relationship of COPD exacerbation severity and frequency on risks for future events and economic burden in the medicare fee-for-service population. International Journal of Chronic Obstructive Pulmonary Disease. 2022 Mar 20:593-608.
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ratios that is based on United States data.[4] This study estimates standardized mortality ratios compared to those without COPD as 1.6 for moderate COPD and 2.7 for severe COPD. As ICER's assessments are conducted for an American audience and meant to drive decision making within the United States health care system, the paper based on United States data would be the more accurate source.

Finally, ICER's health state utility values are derived from a randomized clinical trial when real world data is available and more accurate. ICER uses utility scores of 0.787 for moderate, 0.750 for severe and 0.647 for very severe COPD. These are second hand and taken from a multi-center randomized clinical trial (RCT) using the UK value set[5]. Over the years, PIPC has laid out the many limitations that result from using utility data derived solely from the trial setting. RCT populations are generally much healthier than real-world disease-specific populations.[6] There are always explicit and implicit exclusion criteria for recruitment into trial settings,[7] including age, the existence of co-morbidities[8] and levels of healthcare access and utilization, that make RCT populations rarely representative of real-world populations of need.[9, 10]

In addition, utilities in RCTs tend to be inflated compared to non-RCT samples of patients[11] as EQ5D gains are often generated for patients in RCTs that are non-disease or treatment related socio-emotive components, that can occur because of receiving greater care and attention from healthcare professionals. There is also a placebo effect from patients in both arms of the trial. Numerous studies have highlighted the utilities generated in RCTs are generally much higher than the equivalents would be for a real-world population.[12]

Ultimately, ICER should be looking to use the best possible sources that are most representative of the population in need of treatment. This should include prioritizing sources based on United States data, large sample sizes, real-world data, and the most recent publications.

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Evidence suggests that frequency of exacerbations is related to significantly worse survival outcomes, a dynamic that is not captured in ICER's model.

Exacerbations, whether treated or untreated, have a detrimental and prolonged impact on patients' health status and outcomes,[13,14] and have cumulative negative effects on lung function over time.[15] COPD exacerbations are highly heterogeneous, varying in severity and phenotype. Evidence has shown that exacerbations are related to worse survival outcomes,[16] yet the model only bases risk of mortality modifiers on severity level, not rate of exacerbations. The frequency of exacerbations is also a marker of both disease burden and mortality risk.[17] Frequent exacerbations, mainly in patients with severe COPD, accelerate disease progression and mortality.[18] This is a dynamic also ignored in the ICER model.

Exacerbations of COPD also have a cumulative effect on lung function. Patients in the 3-year TORCH study who experienced 0–1.0 moderate to severe exacerbations per year had a 37% faster decline in lung function than those with no exacerbations. Among those patients who experienced more than one moderate to severe exacerbation, the rate of decline in lung function was 65% faster.[3] Rate of exacerbations also varies strongly not just by severity but also by age and gender[19], the dynamic nature of which is not adequately represented using a single estimate of exacerbations per cycle used in the model.

The ICER model largely ignores the complexity of this dynamic between lung function and exacerbation rate over time, and the impact of exacerbation rate on mortality and disease progression. This is a stark omission, as it will not allow ICER's assessment to capture an accurate value of treatment of COPD.

ICER Continues to Use the Discriminatory QALY and the Similar Measure evLYG.

Multiple studies have shown that cost-effectiveness models using the quality-adjusted life year (QALY) discriminate against patients with chronic conditions, [20] like COPD, and people with disabilities.[21] There is widespread recognition that the use of the QALY is discriminatory,

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reflected in laws that bar its use in government decision-making. The National Council on Disability (NCD), an independent federal agency advising Congress and the administration on disability policy, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.[22]

Additionally, we share the concerns of NCD about the equal value of life year gained (evLYG), a similar measure created by ICER to supplement the QALY. The evLYG is a simplistic fix attempting to address criticism that the QALY devalues life years lived with a disability, yet it fails to account for oversimplified measures of quality-of-life gains in expected life years (not extended life years) and it does not account for any health improvements in extended life years. Like the QALY, the evLYG relies on average estimates based on generic survey data and obscures important differences in patients' clinical needs and preferences, particularly those with complex diseases and from underrepresented communities.[23] It assumes that people value life year gains more than quality of life improvements, giving a lower value to health interventions in patient populations that have a lower life expectancy or fewer life years gained from treatment, which may include people with disabilities, underlying chronic conditions, the elderly, and certain communities of color.[24] With the evLYG and the QALY, ICER promotes two compromised and flawed measures of health gain. Deciding which to choose is confusing and inconsistent.

ICER fails to capture the heterogeneous nature of COPD.

As ICER notes in its report, COPD is a widely heterogenous disease[25] both in terms of the cause, the level of comorbidity,[26] and its impact on patient experience.[27] This points to a larger issue with respect to value assessment reporting is that the archetypal cost-effectiveness model relies heavily on producing effect size based on population averages, and rarely are results specific to subpopulations released in results.[28] It is well established that generating and reporting of

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differential value assessment across subgroups leads to substantial health gains, both through treatment selection and coverage.[29,30]

If ICER is to take seriously its role of informing health policy decision makers about the value of new therapies, it needs to move away from the assumption that all patients are the same. No patient is average, and it is essential that ICER moves to acknowledge this and incorporate analysis of subpopulations and produce ranges of value rather than relying on an archetypal patient.

Conclusion

PIPC urges ICER to reconsider both its data sources and modeling choices if it seeks to provide an accurate representation of value to patients with COPD. Where available, real-world evidence based on United States populations should be relied on in the model. ICER must also move away from using discriminatory metrics and the antiquated practice of looking at value to an "average" patient.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

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