SM Journal of Family Medicine ISSN: 2576-0262

Mini Review

Clinical Therapeutics: In Which Patients with COPD Should Ensifentrine be Added to Standard Therapy?

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WHY THIS TOPIC IS IMPORTANT

Despite advances in inhaled bronchodilator therapy, many patients with Chronic Obstructive Pulmonary Disease (COPD) remain symptomatic and experience activity limitation despite appropriate use of long-acting β_2-agonists (LABAs), Long-Acting Muscarinic Antagonists (LAMAs), and Inhaled Corticosteroids (ICS). Ensifentrine represents a novel dual-mechanism option that may address persistent dyspnea and inflammation in this population.

WHAT IS ENSIFENTRINE AND HOW DOES IT WORK?

Ensifentrine (brand name Ohtuvayre) is a first-in-class inhaled dual Phosphodiesterase (PDE) 3 and 4 inhibitor, approved by the U.S. Food and Drug Administration in 2024 as twice-daily maintenance therapy for COPD. By blocking PDE3 and PDE4, ensifentrine increases intracellular Cyclic Adenosine Monophosphate (cAMP), resulting in bronchodilation and anti-inflammatory effects [1].

- Bronchodilation results from inhibition of PDE3 in airway smooth muscle, increasing cAMP and promoting relaxation.

- Anti-inflammatory activity arises from PDE4 inhibition in inflammatory cells (neutrophils, eosinophils, macrophages, lymphocytes, and fibroblasts), leading to reduced cytokine release [2-4].

Unlike inhaled corticosteroids, which demonstrate limited efficacy against neutrophilic inflammation in COPD due to reduced histone deacetylase 2 activity, ensifentrine directly suppresses cytokines such as IL-8 and TNF-α. Additionally, PDE4 inhibition activates the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), improving mucociliary clearance.

WHERE DOES ENSIFENTRINE FIT IN THE CURRENT TREATMENT LANDSCAPE?

The GOLD 2025 guidelines recommend a stepwise approach beginning with dual long-acting bronchodilators, with ICS reserved for patients with frequent exacerbations or blood eosinophil counts ≥300 cells/μL.

Ensifentrine is not a replacement for guideline-directed inhaled therapies but may be considered as an adjunctive maintenance option for patients with persistent dyspnea or activity limitation despite optimized inhaler use.

WHAT DOES THE EVIDENCE SHOW?

Approval of ensifentrine was based on the ENHANCE-1 and ENHANCE-2 phase 3 trials, which enrolled over 1,500 patients with moderate-to-severe COPD (GOLD grades 2–3).

KEY FINDINGS

- FEV_1 improvement: +87 mL in ENHANCE-1 and +94 mL in ENHANCE-2 vs placebo.

- Exacerbations: 36–43% reduction in moderate-to-severe exacerbations across studies.

- Quality of life: 2–3 point improvement in St. George's Respiratory Questionnaire (SGRQ).

- Adverse events: Similar to placebo, with minimal gastrointestinal effects [5].

Benefits were observed regardless of background therapy (LAMA, LABA, or ICS). Although pooled data demonstrated a 36% reduction in moderate-to-severe exacerbations, this was not a prespecified primary endpoint. Accordingly, GOLD 2025 characterizes these findings as suggestive but requiring confirmation in targeted populations.

ADMINISTRATION AND PRACTICAL CONSIDERATIONS

Ensifentrine is delivered as a nebulized solution (0.75 mg/3 mL per dose) twice daily using a jet nebulizer, with each session lasting approximately five minutes. It should be administered separately from other nebulized medications to avoid drug stability issues. Minimal systemic absorption contributes to its favorable side-effect profile.

WHO ARE THE IDEAL CANDIDATES?

Ensifentrine is best thought of as a *symptom-focused add-on therapy* for moderate to severe COPD patients who remain short of breath despite appropriate inhaler use.

LIMITATIONS AND FUTURE DIRECTIONS

- Long-term safety beyond one year remains under investigation.

- Mortality benefit has not been demonstrated.

- Cost and access may initially limit use.

Submitted: 22 November, 2025 | **Accepted:** 06 January, 2026 | **Published:** 07 January, 2026

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Citation: Chapa-Rodriguez A, Abou-Elmagd T, Hafiz Sarwar (2026) Clinical Therapeutics: In Which Pa-tients with COPD Should Ensifentrine be Added to Standard Therapy?. SM J Fam Med 4(1)-2.

- Comparative effectiveness versus roflumilast or biologic therapies is unknown.

- Future trials should evaluate its role as a steroid-sparing agent or in patients intolerant to ICS.

HOW DOES ENSIFENTRINE DIFFER FROM ROFLUMILAST?

Feature	Ensifentrine	Roflumilast
Mechanism	Dual PDE3/4 inhibition	PDE4 inhibition only
Route	Inhaled (nebulized)	Oral
Primary actions	Bronchodilation + anti-inflammatory	Anti-inflammatory only
Tolerability	Minimal GI effects	Frequent nausea, diarrhea, weight loss

PRACTICAL POINTS FOR CLINICIANS

1. Confirm inhaler technique and adherence before escalation.

2. Consider ensifentrine for patients with persistent dyspnea despite optimized therapy.

3. Continue existing maintenance regimen; ensifentrine is adjunctive.

4. Reassess response after 3–6 months.

5. Address cost and insurance coverage early.

KEY TAKEAWAYS

- Ensifentrine is the first inhaled dual PDE3/4 inhibitor for COPD.

- Improves lung function and symptoms with a placebo-like safety profile.

- Appropriate for symptomatic GOLD 2–3 patients who remain dyspneic despite optimized inhaler therapy.

- Long-term safety and comparative efficacy data are awaited.

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