Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCRES021.0625	**RESPIRATORY AGENTS** **OHTUVAYRE™** (ensifentrine inhalation suspension)
Effective Date: 8/1/2025	**Review/Revised Date**: 04/25 (snm)
Original Effective Date: 01/25	**P&T Committee Meeting Date**: 10/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

REQUIRED MEDICAL INFORMATION:
For initial authorization:
1. Documented diagnostic spirometry confirming chronic obstructive pulmonary disease (COPD)
2. One of the following:
    a. Documented inadequate response to a 60-day trial of dual therapy with a formulary combination of a long-acting muscarinic antagonist and long-acting beta agonist (LAMA and LABA), or triple therapy with Trelegy Ellipta®. Inadequate response is defined as persistent exacerbations or uncontrolled symptoms (such as dyspnea, chronic cough, sputum production, wheezing, chest tightness) despite ongoing treatment.
    b. Documented contraindication or intolerance to all formulary LAMA/LABA combination inhalers and triple therapy inhalers (Trelegy®).

For reauthorization: Response to therapy indicating improvement or stabilization of condition

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication.

PRESCRIBER RESTRICTIONS: N/A

COVERAGE DURATION:
Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
Two ampules per day

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:
Ensifentrine (Ohtuvayre™) is approved for maintenance treatment of chronic obstructive pulmonary disease (COPD) in adults. It is a dual inhibitor of phosphodiesterase-3 (PDE3) and phosphodiesterase-4 (PDE4), increasing bronchodilation and decreasing inflammation. Recommended dose is 3 mg (one unit-dose ampule) twice daily, once in the morning and once in the evening, administered by oral inhalation using a standard jet nebulizer with a mouthpiece.

FDA APPROVED INDICATIONS:
- Maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

POSITION STATEMENT:
Current guidelines

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 Report supports the initiation of ensifentrine in patients who are already taking maintenance treatment and are experiencing persistent dyspnea.[4]

Safety and efficacy of Ohtuvayre™

- Two phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter trials (ENHANCE-1 N=763, ENHANCE-2 N=790) compared twice-daily ensifentrine 3mg versus placebo via standard jet nebulizer over 24 weeks, and over 48 weeks for a safety subset in the first trial.[5]
- Efficacy:
    - Ensifentrine significantly improved average FEV_1 area under the curve at 0-12 hours versus placebo in both trials.
        - ENHANCE-1: 87 mL (95% CI 55-119; $p < 0.001$)
        - ENHANCE-2: 94 mL (95% CI 65-124; $p < 0.001$)
    - Ensifentrine significantly improved Week 12 peak FEV_1 from baseline versus placebo in both trials.
        - ENHANCE-1: 147 mL (95% CI 111-183; $p < 0.001$)
        - ENHANCE-2: 146 mL (95% CI 113-179; $p < 0.001$)
    - Ensifentrine significantly reduced the rate of moderate or severe exacerbations versus placebo over 24 weeks in both trials.
        - ENHANCE-1: rate ratio = 0.64 (95% CI 0.40-1.00; $p = 0.050$)
        - ENHANCE-2: rate ratio = 0.57 (95% CI 0.38-0.87; $p = 0.009$)
    - Ensifentrine significantly increased time to first exacerbation.
        - ENHANCE-1: hazard ratio = 0.62 (95% CI 0.39-0.97; $p = 0.038$)
        - ENHANCE-2: hazard ratio = 0.58 (95% CI 0.38-0.87; $p = 0.009$)
        - Ensifentrine only showed statistically improved quality of life measures in some measures and/or in only one of the trials.
- Safety: Ensifentrine was well tolerated in both trials with similar rates of adverse events and discontinuation compared to placebo.
- Limitation: Exclusions included patients on LABA+LAMA, LABA+LAMA+ICS, and patients with asthma, which are considerable populations of interest and leaves uncertainty regarding ensifentrine's place in therapy.

Cost Effectiveness of Ohtuvayre™

- Institute for Clinical and Economical Review (ICER) concluded that compared to no therapy, LAMA, or LABA, with or without ICS, patients with moderate to severe COPD on ensifentrine experienced decreased exacerbations and increased QALYs, evLYs, and life years.
- Ensifentrine's WAC and incremental cost-effectiveness ratios are $35,400 per year, $492,000 per QALY gained, and $426,000 per evLY gained.

- While demonstration of increased day-to-day quality of life of patients with COPD would improve ensifentrine's cost-effectiveness, its WAC would still be higher than commonly used cost-effectiveness thresholds at $35,400 versus $7,500 to $12,700 respectively.
- ICER has "high certainty" that ensifentrine provides "at least a small net health benefit, and may result in substantial net health benefit" as an add-on to maintenance therapy versus maintenance therapy alone, with an evidence rating of B+.

BILLING GUIDELINES AND CODING:

Drug CODE*		
HCPCS	J7601	Ensifentrine, inhalation suspension, fda approved final product, non-compounded, administered through dme, unit dose form, 3 mg

*Coding Notes:
• The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
• HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCE/RESOURCES:

1. Ohtuvarye™ (ensifentrine). Package Insert. Verona Pharma; 2024.
2. Ohtuvarye™ (ensifentrine). In: Micromedex [proprietary data]. Merative LP; 2024. Accessed April 25, 2025.
3. Ohtuvarye™ (ensifentrine). In: Lexi-Drugs [proprietary data]. UpToDate Inc; 2024. Accessed April 25, 2025.
4. Global Initiative for Chronic Obstructive Lung Disease. *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*. Global Initiative for Chronic Obstructive Lung Disease; 2025. Accessed April 25, 2025. https://goldcopd.org/
5. Anzueto A, Barjaktarevic IZ, Siler TM, et al; ENHANCE investigators. Ensifentrine, a novel phosphodiesterase 3 and 4 inhibitor for the treatment of chronic obstructive pulmonary disease: randomized, double-blind, placebo-controlled, multicenter phase iii trials (the ENHANCE Trials). *Am J Respir Crit Care Med*. 2023;208(4):406-416. doi:10.1164/rccm.202306-0944OC
6. Lin G, Whittington MD, Wright A, McKenna A, Richardson M, Rind DM. *Ensifentrine for the Treatment of Chronic Obstructive Pulmonary Disease: Effectiveness and Value*. Institute for Clinical and Economic Review; 2024.

Accessed April 25, 2025. https://icer.org/wp-content/uploads/2023/11/ICER_COPD_Final-Report_For-Publication_071624.pdf