Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCRES021.1024	**RESPIRATORY AGENTS** **OHTUVAYRE™** (ensifentrine inhalation suspension)
Effective Date: 1/1/2025	**Review/Revised Date**:
Original Effective Date: 01/25	**P&T Committee Meeting Date**: 10/24
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:
1. Documented diagnostic spirometry confirming 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®).

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. FDA-labeled dosing will be approved until no longer eligible with the plan, subject to formulary and/or benefit changes.

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 patients aged 18 years and older.
- Limitation: Ensifentrine is NOT indicated for the relief of acute bronchospasm.

POSITION STATEMENT:
Current guidelines
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 Report supports inhaled corticosteroid (ICS) in combination with one or two long-acting bronchodilators (LAMA or LABA) for patients with:

  - History of hospitalization(s) for exacerbations of COPD, despite appropriate long-acting bronchodilator maintenance therapy
  - Two or more moderate exacerbations of COPD per year, despite appropriate long-acting bronchodilator maintenance therapy
  - Blood eosinophils greater than 300 cells/microliter; and/or
  - History of, or concomitant, asthma[4]
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines support initiation of triple therapy with an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist bronchodilators (LAMA) and a long-acting beta agonist (LABA) as an option for patients with:
  - Persistent breathlessness or exercise limitations on LABA/ICS
  - Continued exacerbations on LABA/LAMA or LABA/ICS[4]
- The GOLD guidelines support the following options for patients on LABA/LAMA/ICS triple therapy, or if blood eosinophils are less than 100, who still have exacerbations:
  - Roflumilast, a PDE4 inhibitor, if force expiratory volume in one second (FEV1) is less than 50% and patient experiences chronic bronchitis
  - Macrolides, preferably azithromycin, especially in former smokers[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.
- 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) evaluated 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+.

REFERENCE/RESOURCES:

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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; 2024. Accessed August 31, 2024. https://goldcopd.org/2024-gold-report/#
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8. Institute for Clinical and Economic Review. *Ensifentrine for the Treatment of Chronic Obstructive Pulmonary Disease: Final Policy Recommendations*. Institute for Clinical and Economic Review; 2024. Accessed August 31, 2024. https://icer.org/wp-content/uploads/2024/07/ICER_COPD_Policy-Recommendations_07162024.pdf