ensifentrine (Ohtuvayre™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO306

Description

Ensifentrine (Ohtuvayre) is a nebulized inhibitor of phosphodiesterase (PDE) 3 and PDE4.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ensifentrine (Ohtuvayre)	Chronic Obstructive Pulmonary Disease (COPD)	3 mg/2.5 mL ampule	150 mL/30 days

Initial Evaluation

I. **Ensifentrine (Ohtuvayre)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A confirmed diagnosis of moderate to severe **Chronic Obstructive Pulmonary Disease (COPD)** when all the following are met:
      1. FEV_1/FVC ratio of < 0.7; **AND**
      2. Post-bronchodilator FEV_1 % predicted of ≥ 30% and ≤ 80%; **AND**
      3. Modified Medical Research Council (mMRC) dyspnea score of ≥ 2; **AND**
   C. Member is currently on triple therapy with a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), and an inhaled corticosteroid [ICS] (e.g., Asmanex); **OR**
   D. Triple therapy with a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), and an inhaled corticosteroid [ICS] (e.g., Asmanex) has been ineffective, not tolerated, or all are contraindicated; **OR**
   E. Eosinophil level is < 100 cells/µL and member is currently on dual therapy with a long-acting beta-2 agonist [LABA] and a long-acting muscarinic antagonist [LAMA] unless ineffective, not tolerated, or all are contraindicated; **AND**
   F. Dual or triple therapy [a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), ± an inhaled corticosteroid [ICS] (e.g., Asmanex)] will be continued in combination with ensifentrine (Ohtuvayre), unless not tolerated or all are contraindicated.

II. Ensifentrine (Ohtuvayre) is considered investigational when used for all other conditions, including but not limited to:
   A. Asthma
   B. Cystic Fibrosis
   C. Non-Cystic Fibrosis Bronchiectasis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., improved dyspnea, improved lung function] **AND**
IV. Dual or triple therapy [a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), ± an inhaled corticosteroid [ICS] (e.g., Asmanex)] will be continued in combination with ensifentrine (Ohtuvayre), unless not tolerated or all are contraindicated.

Supporting Evidence

I. Ensifentrine (Ohtuvayre) was studied in multicentered, randomized, double-blind, parallel-group, placebo-controlled duplicative trials, ENHANCE-1 and ENHANCE-2 for 24 weeks. Patients were randomized to receive either ensifentrine (Ohtuvayre) 3mg or placebo. Patients were also allowed to continue their maintenance therapies.
II. The primary efficacy outcome was the average change from baseline forced expiratory volume (FEV1) area under the curve $(AUC)_{0\text{-}12h}$ at week 12. Stratified secondary endpoints include peak FEV1 at week 12, E-RS total score at week 24, SGRQ total score at week 24, and morning trough FEV1 at week 12. The primary outcome was met in both trials with an FEV1 change from baseline of 61mL on ensifentrine (Ohtuvayre) and -26mL on placebo (difference of 87mL [95% CI, 55 to 119; $p<0.001$]) for ENHANCE-1 and 48mL on ensifentrine (Ohtuvayre) and -46mL on placebo (difference of 94mL [95% CI, 64 to 124; $p<0.001$]) for ENHANCE-2.
III. The improvement in FEV1 is statistically significant compared to placebo Although it is a modest change from baseline, there were associated improvements in symptoms and exacerbation rates. A pooled data analysis of ENHANCE-1 and ENHANCE-2 completed by the manufacturer and independently verified by the Institute for Clinical and Economic Review (ICER) group saw a 41% reduction in exacerbation rates and a 41% reduction in time to first exacerbation event compared to placebo at week 24. Collectively, there's moderate confidence that ensifentrine (Ohtuvayre) provides a clinically meaningful benefit to patients in the treatment of

COPD, providing a similar overall treatment profile to standard of care agents (LAMA/LABA ± ICS).

IV. Nasopharyngitis and upper respiratory tract infections were the most commonly reported adverse events. The pooled incidence rates for nasopharyngitis were 2.6% vs. 0% and for upper respiratory tract infections, 1.8% vs. 0% for ensifentrine (Ohtuvayre) and placebo, respectively. There was a total of 14 deaths reported that were considered treatment-emergent but occurred across both ensifentrine and placebo arms.

V. The 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report defines diagnosis of COPD as any patient with a post-bronchodilator FEV1/FVC ratio of <0.7, along with characteristic symptoms such as dyspnea, cough or sputum production, and/or history of exposure to risk factors (i.e. tobacco smoke, occupational contact, host factors). Spirometry also provides guidance on severity of airflow obstruction and disease.

Grade	Severity	FEV1 % predicted
GOLD 1	Mild	≥80
GOLD 2	Moderate	50-79
GOLD 3	Severe	30-49
GOLD 4	Very Severe	<30

VI. The modified Medical Research Council (mMRC) dyspnea scale provides a measure of breathlessness in patients with COPD and relates to other comprehensive health status measures such as the St. George's Respiratory Questionnaire (SGRQ). An mMRC score of ≥ 2 is considered the threshold for less or more breathlessness.

VII. As of the 2024 GOLD Report, the ABE Assessment Tool is a way to determine current disease severity and how to approach treatment based on symptom scores such as the mMRC, severity of airflow obstruction, and exacerbation history. Depending on the severity category, the recommended initial treatment includes a long-acting beta-adrenoceptor agonist (LABA) and/or long-acting muscarinic agent (LAMA) with, or without, an inhaled corticosteroid (ICS). If control is not achieved despite proper adherence to initial regimen, further recommendations include maximizing LAMA and LABA dual therapy, addition of ICS for triple therapy if needed, addition of a PDE inhibitor for patients experiencing increased exacerbations and maximizing non-pharmacological treatment. Treatment is focused on reducing symptoms and exacerbations and FEV1 change is considered a surrogate marker to assess disease decline rate. Long-acting beta-adrenoceptor agonist (LABA) and LAMA therapies are found to reduce rate of exacerbations alone or in combination.

VIII. Addition of ICS therapy to an existing regimen was found to have a greater impact on lung function and reduction of exacerbations vs. ICS alone. Inclusion of an ICS is primarily reserved for cases that have higher exacerbation rates per year, history of asthma, hospitalizations due to exacerbations and eosinophilic disease (blood eosinophils > 100 cells/µL). The benefits should outweigh the risks; addition of an ICS may cause increased risk of steroid-related diseases and increased risk of pneumonia.

IX. In both pivotal trials ensifentrine (Ohtuvayre) was studied as an add on to background therapies, (a mix of LABA or LAMA, with or without an ICS) in the majority of patients. Although background therapies did not reflect the guideline standard of dual LAMA/LABA or triple therapy (LAMA/LABA/ICS), ensifentrine (Ohtuvayre) is likely to be utilized as add-on therapy to LAMA/LABA ± ICS in real-world practice, given the need for additional treatment options in this setting.

Investigational Uses

I. Ensifentrine (Ohtuvayre) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   a. Asthma
      i. Ensifentrine (Ohtuvayre) was studied in a phase II, randomized, double-blind, placebo controlled seven-way crossover study (PMID: 31202957; NCT02427165) to assess the effect of a single dose of ensifentrine against placebo and salbutamol (a beta-2 agonist). Co-primary endpoints were peak and average FEV1 over 12 hours compared to placebo and salbutamol. All active treatments were found superior to placebo with no significant difference between ensifentrine and salbutamol. The safety profile was similar to salbutamol. The treatments were seven separate visits with a 2–14-day washout period in between. Further studies are required to assess the true long-term efficacy and safety as a background asthma controller therapy.
   b. Cystic Fibrosis
      i. A phase IIa, randomized, double blind, placebo controlled, three-way crossover study (NCT02919995) to assess the pharmacokinetics in adult patients with cystic fibrosis (CF). Interventions included two different doses of ensifentrine and placebo with the primary outcome as AUC by dose and maximum plasma concentration after each dose. Secondary outcome measures included FEV1 AUC at different time points. There was a dose-dependent correlation between drug concentration and AUC when comparing the higher to lower dose ensifentrine, while the time to maximum concentration was similar. The mean secondary peak FEV1 between all three treatments were similar. Further studies are needed to compare therapy with patients who are on standard of care CF medications to understand the true benefit as possibly an add-on treatment.
   c. Non-Cystic Fibrosis Bronchiectasis
      i. This is currently in review for treatment of non-cystic fibrosis (non-CF) bronchiectasis. In theory, the dual anti-inflammatory and bronchodilator action can reduce cough and sputum symptoms along with reducing respiratory inflammation and exacerbations related to bronchiectasis. Further RCT studies

are required to assess the long-term efficacy and safety versus placebo and/or other standard of care therapies.

References

1. Ohtuvayre [Prescribing Information]. London, UK and Raleigh, NC: Verona Pharma. June 2024.
2. Anzueto A, Barjaktarevic IZ, Siler TM, et al. 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.202306-0944OCTitle
3. Global Initiative for Chronic Obstructive Lung Disease. 2024 REPORT Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease Global Initiative for Chronic Obstructive Lung Disease Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.; 2024. https://goldcopd.org/wp-content/uploads/2024/02/GOLD-2024_v1.2-11Jan24_WMV.pdf
4. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014 Feb 1;189(3):250-5. doi: 10.1164/rccm.201310-1863PP. PMID: 24383418

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
dupilumab (Dupixent®) Policy	Chronic Obstructive Pulmonary Disease (COPD)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2024