LOUISIANA BLUE

ensifentrine (Ohtuvayre™)

Policy # 00913
Original Effective Date: 02/01/2025
Current Effective Date: 02/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider ensifentrine (Ohtuvayre™)‡ for the treatment of chronic obstructive pulmonary disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for ensifentrine (Ohtuvayre) for the treatment of chronic obstructive pulmonary disease will be considered when the following criteria are met:

- Patient has a diagnosis of chronic obstructive pulmonary disease (COPD); AND
- Diagnosis of COPD has been confirmed with spirometry demonstrating a post-bronchodilator FEV_1/FVC ratio less than 0.7; AND
- Patient has moderate to severe airflow obstruction as evidenced by post-bronchodilator FEV_1 $\geq$ 30% and $\leq$ 70% of predicted normal; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient is 18 years of age and older; AND
- Patient has clinically impactful symptoms defined by one of the following:
  - A COPD Assessment Test (CAT) score greater than or equal to 10; OR
  - A modified Medical Research Council (mMRC) dyspnea scale grade 2 or higher; AND

  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has tried and failed 3 months of therapy with ONE of the following unless there is clinical evidence or patient history that suggests the use of these therapies will be ineffective or cause and adverse reaction to the patient:
  - Long-acting beta-2 agonist (LABA) plus long-acting muscarinic antagonist (LAMA) dual therapy; OR

  - Long-acting beta-2 agonist (LABA) plus long-acting muscarinic antagonist (LAMA) plus inhaled corticosteroid (ICS) triple therapy; AND

  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient will continue use of maintenance background therapies along with Ohtuvayre; AND
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Ohtuvayre will not be used in combination with Daliresp®‡ (roflumilast).

(Note: Examples of inhaled therapies used for COPD include: LABA products such as Serevent®‡ Diskus [salmeterol xinafoate], Striverdi®‡ Respimat [olodaterol], Brovana®‡ [arformoterol tartrate, generic], and Perforomist®‡ [formoterol fumarate], LAMA products such as Incruse®‡ Ellipta [umeclidinium], Spiriva®‡ HandiHaler [tiotropium bromide], Spiriva® Respimat [tiotropium bromide], Tudorza®‡ Pressair [aclidinium bromide], and Yupelri®‡ [revefenacin], and combination therapies such as Anoro™‡ Ellipta [umeclidinium and vilanterol], Bevespi Aerosphere™‡ [glycopyrrolate and formoterol fumarate], Duaklir®‡ Pressair [aclidinium bromide and formoterol fumarate], Stiolto® Respimat [tiotropium bromide and olodaterol], Advair Diskus®‡ [fluticasone propionate and salmeterol], Breo®‡ Ellipta [fluticasone furoate and vilanterol], Symbicort®‡ [budesonide and formoterol fumarate], Breztri Aerosphere™‡ [budesonide, glycopyrrolate, and formoterol fumarate], and Trelegy Ellipta [fluticasone furoate, umeclidinium, and vilanterol]).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of ensifentrine (Ohtuvayre) when any of the following patient selection criteria are NOT met to be **not medically necessary:****

- Patient has moderate to severe airflow obstruction as evidenced by post-bronchodilator FEV1 ≥ 30% and ≤ 70% of predicted normal
- Patient has clinically impactful symptoms defined by one of the following:
  - A COPD Assessment Test (CAT) score greater than or equal to 10; OR
  - A modified Medical Research Council (mMRC) dyspnea scale grade 2 or higher
- Patient has tried and failed 3 months of therapy with ONE of the following:
  - Long-acting beta-2 agonist (LABA) plus long-acting muscarinic antagonist (LAMA) dual therapy; OR
  - Long-acting beta-2 agonist (LABA) plus long-acting muscarinic antagonist (LAMA) plus inhaled corticosteroid (ICS) triple therapy
- Patient will continue use of maintenance background therapies along with Ohtuvayre

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When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of ensifentrine (Ohtuvayre) when the patient selection criteria are not met (EXCEPT those denoted as **not medically necessary****)** to be **investigational.***

Based on review of available data, the Company considers the use of ensifentrine (Ohtuvayre) for any non-FDA approved indication to be **investigational.***

Background/Overview

Ohtuvayre is a phosphodiesterase 3 (PDE3) inhibitor and phosphodiesterase 4 (PDE4) inhibitor indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients. It is available as a 3 mg ampule that is administered by oral inhalation using a standard jet nebulizer twice daily.

COPD is a chronic lung condition that is characterized by respiratory symptoms stemming from abnormalities in the airways, which often cause bronchitis and bronchiolitis, and/or from the alveoli, which often causes emphysema. Common symptoms of COPD include dyspnea, wheezing, chest tightness, and a cough that may or may not present with sputum production. Diagnosis of COPD is confirmed with spirometry demonstrating that airflow limitation is either irreversible or only partially reversible as defined by a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio less than 0.7. Treatment regimens are typically based on an assessment of symptoms and exacerbation history, often guided by two validated patient questionnaires. The COPD Assessment Test, or CAT, is a patient questionnaire that assesses multiple symptoms and other aspects of COPD, while the modified Medical Research Council (mMRC) dyspnea scale only assesses dyspnea. A score of 10 or greater on the CAT is indicative of clinically impactful symptoms, meaning more impact from COPD on a patient's life. A score of 2 or more on the mMRC dyspnea scale denotes clinically impactful breathlessness meaning that dyspnea is increasingly affecting a patient's daily functions as the score increases. Long-acting bronchodilators, including long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and combination products containing both of these classes are the mainstay of maintenance treatment for this condition. Inhaled corticosteroids in combination with a LABA and LAMA are considered for those who have a blood eosinophil level ≥ 300 cells/microliter. Daliresp (roflumilast), an oral PDE4 inhibitor, systemic corticosteroids, antibiotics, and mucolytics may also be considered in select patients. Ohtuvayre is the first PDE3 and PDE4 inhibitor approved for COPD.

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COPD Assessment Test

	Score						
	0	**1**	**2**	**3**	**4**	**5**	
I never cough							I cough all the time
I have no phlegm (mucus) in my chest at all							My chest is completely full of phlegm (mucus)
My chest does not feel tight at all							My chest feels very tight
When I walk up a hill or one flight of stairs, I am not breathless							When I walk up a hill or one flight of stairs, I am very breathless
I am not limited doing any activities at home							I am very limited doing activities at home
I am confident leaving my home despite my lung condition							I am not at all confident leaving my home because of my lung condition
I sleep soundly							I don't sleep soundly because of my lung condition
I have lots of energy							I have no energy at all
							Total Score:

Modified Medical Research Council Dyspnea Scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessnes or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards (91 meters) or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Ohtuvayre is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

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The efficacy of Ohtuvayre was evaluated in two 24-week randomized, double-blind, placebo-controlled, parallel-group clinical trials (ENHANCE-1 and ENHANCE-2). The two trials enrolled a total of 1553 adults 40 to 80 years of age with moderate to severe COPD. The two trials were identical with the exception that ENHANCE-1 was 48 weeks in length due to including an additional 24-week safety extension. Patients were randomized 5:3 to receive Ohtuvayre 3 mg or placebo twice daily inhaled via a standard jet nebulizer for 24 weeks. The primary efficacy endpoint was the mean change from baseline to Week 12 in the FEV_1 area under the concentration-time curve over 12 hours ($AUC_{0\text{-}12h}$). In both trials, Ohtuvayre demonstrated a statistically significant improvement in FEV_1 $AUC_{0\text{-}12h}$ compared to placebo.

References

1. Ohtuvayre [package insert]. Verona Pharma, Inc. Raleigh, North Carolina. Updated June 2024.
2. Ohtuvayre (ensifentrine). IPD Analytics. Updated August 2024.
3. Modified Medical Research Council (mMRC) dyspnea scale. UpToDate. Accessed January 2025.
4. Calculator: COPD Assessment Test (CAT). UpToDate. Accessed January 2025.

Policy History

Original Effective Date: 02/01/2025
Current Effective Date: 02/01/2025
01/02/2025 Medical Policy Committee review
01/08/2025 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 01/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.