PHARMACY COVERAGE GUIDELINE

OHTUVAYRE™ (ensifentrine) inhalation oral suspension Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Ohtuvayre (ensifentrine) inhalation oral suspension and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of moderate to severe chronic obstructive pulmonary disease (COPD) for maintenance treatment

  4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:

a. Has a modified Medical Research Council dyspnea scale score greater than or equal to 2 or COPD assessment Test (CAT) greater than or equal to 10 (see Definitions section)
b. Pre- and post-albuterol/salbutamol FEV1/FVC ratio of <0.70
c. Post-albuterol/salbutamol FEV1 ≥30 % and ≤70% of predicted normal

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual continues to experience persistent dyspnea related to COPD or has experienced at least 1 exacerbation in the previous year (exacerbation is defined as any hospitalization or emergency department visit or need for a new prescription for oral steroids or antibiotics for COPD exacerbation)

7. Individual is on **TWO** of the following treatments for COPD: (see Definitions section)
   a. LAMA-LABA dual bronchodilator therapy
   b. LABA-ICS dual bronchodilator therapy
   c. LAMA-LABA-ICS triple bronchodilator therapy

8. Individual is not using Ohtuvayre for acute symptoms of bronchospasm or a rescue therapy for treatment of acute episodes of bronchospasm

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Ohtuvayre (ensifentrine) inhalation oral suspension and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Pulmonologist

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
   a. Significant improvement from baseline in FEV1
   b. Reduction in the number of moderate or severe exacerbation
   c. Reduction in daily rescue medication use
   d. Delay in the time to next moderate or severe exacerbation
   e. Individual has experienced improvements in persistent shortness of breath, sputum production, and cough

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant paradoxical bronchospasm from Ohtuvayre use

6. Individual is not using Ohtuvayre for acute symptoms of bronchospasm or a rescue therapy for treatment of acute episodes of bronchospasm

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

Description:

Ohtuvayre (ensifentrine) inhalation oral suspension is a phosphodiesterase 3 (PDE3) inhibitor and phosphodiesterase 4 (PDE4) inhibitor indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult individuals.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Modified Medical Research Council (mMRC) 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 breathlessness or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards of after a few minutes on level ground
4	I am too breathless to leave the house, or I am breathless when dressing

COPD Assessment Test (CAT)

	Circle the number that best describes you	
I never cough	1 2 3 4 5	I cough all the time
I have no phlegm in my chest at all	1 2 3 4 5	My chest is completely full of phlegm
My chest does not feel tight at all	1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	1 2 3 4 5	I am very limited doing activities at home

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I am confident leaving my home despite my lung condition	1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	1 2 3 4 5	I have no energy at all

Follow-up management of COPD*:

Follow-up management of COPD*	
All patients with COPD should have a rapid relief inhaler available, either a SABA or a SABA-SAMA (SABA preferred for patients using a LAMA)	
No exacerbations and no dyspnea/low COPD impact (i.e., mMRC 0 to 1 or CAT <10)¶	
Current therapy	**Actions**
• SABA or SABA-SAMA as needed	▪ Continue current therapy
• LAMA, LABA, or LAMA-LABA	▪ Continue current therapy
• LABA-ICS or LABA-LAMA-ICS	▪ Taper or discontinue ICS dose to reduce adverse effects of ICS[Δ]
Persistent dyspnea or high COPD impact with no exacerbations (i.e., mMRC ≥2 or CAT ≥10)¶	
Current therapy	**Actions**
• SABA or SABA-SAMA as needed	▪ Add LAMA or LABA
• LAMA or LABA monotherapy	▪ Change to LAMA-LABA
• LABA-ICS	▪ Add LAMA for triple therapy LAMA-LABA-ICS ▪ Add LAMA for dual therapy LAMA-LABA if lack response to ICS or adverse effects from ICS
• LAMA-LABA	▪ Substitute alternate delivery system or different LAMA-LABA agents ▪ Trial of LAMA-LABA-ICS, in patients with blood eosinophils ≥100 cells/microL[◊] ▪ Additional interventions may include low-dose theophylline, repeat pulmonary rehabilitation, and nonpharmacologic therapies[§]
• LAMA-LABA-ICS	▪ Continue LAMA-LABA-ICS ▪ Additional interventions may include low-dose theophylline, repeat pulmonary rehabilitation, and nonpharmacologic therapies for COPD[§] ▪ Stop ICS, if initial indication unclear, lack of response, or adverse effect to ICS[Δ]
+/– Persistent dyspnea or high COPD impact & ≥1 exacerbations in past year (i.e., mMRC ≥2 or CAT ≥10)¶	
Current therapy[§]	**Actions**
• SABA or SABA-SAMA as needed	▪ Add LAMA

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• LAMA or LABA monotherapy	▪ Change to LAMA-LABA for dual therapy, if blood eosinophil count <300/microL◊ Or ▪ Add ICS for triple therapy LAMA-LABA-ICS, if blood eosinophil count ≥300/microL◊ or hospitalization for COPD exacerbation Or ▪ Add ICS for dual therapy LABA-ICS, if blood eosinophil count ≥100/microL◊ and LAMA contraindicated
• LAMA-LABA	▪ Add ICS for triple therapy LAMA-LABA-ICS, if blood eosinophil count ≥100/microL◊ Or ▪ Continue LAMA-LABA, if blood eosinophil count <100/microL¥ and add either: ▪ Roflumilast‡ ▪ Azithromycin†
• LABA-ICS	▪ Add LAMA for triple therapy LAMA-LABA-ICS Or ▪ Add LAMA for dual therapy LAMA-LABA if lack of response to ICS or adverse effects from ICSΔ
• LAMA-LABA-ICS	▪ Continue LAMA-LABA-ICS and add either: ▪ Roflumilast‡ ▪ Azithromycin† ▪ Stop ICS if initial indication unclear, lack of response, or adverse effects of ICSΔ

* Adjustments to pharmacologic therapy for COPD are based on an assessment of dyspnea/exercise limitation (mMRC or CAT), frequency of exacerbations, and peripheral blood eosinophil counts. Follow-up visits are also an opportunity to assess and reinforce nonpharmacologic interventions for COPD, including smoking cessation; inhaler technique and adherence to medications; administration of pneumococcal and seasonal influenza vaccinations; pulmonary rehabilitation; and nutrition counselling regarding healthy diet and normal BMI. All patients with COPD should have a rapid relief inhaler available, either a SABA or a SABA-SAMA (SABA preferred for patients using a LAMA).
¶ mMRC dyspnea scale: https://www.pcrs-uk.org/mrc-dyspnoea-scale; CAT evaluates health impact of COPD: https://www.catestonline.org.
Δ If blood eosinophil count ≥300 cells/microL, patient is more likely to experience exacerbations after ICS withdrawal. Close patient monitoring is required if ICS are withdrawn.
◊ In patients with exacerbations and blood eosinophil count ≥300 cells/microL, the addition of ICS is likely to be of benefit. For patients with eosinophil counts ≥100 but <300 cells/microL, ICS may improve exacerbation rates and pulmonary function.
¥ For patients with a blood eosinophil count <100 cells/microL, there is a low likelihood that addition of ICS will be beneficial and higher risk of pneumonia after the addition of ICS.
‡ Roflumilast is used for patients with chronic bronchitis and FEV <50% predicted, particularly if there has been at least 1 hospitalization for an exacerbation in the past year. Potential adverse effects may limit use.
† Azithromycin preventive therapy is more effective in patients who are not current smokers. However, it may lead to development of resistant organisms.
§ Nonpharmacologic measures (e.g., oxygen therapy if SpO ≤88%, pulmonary rehabilitation, bronchoscopic or surgical lung volume reduction, lung transplantation) can help reduce dyspnea and exacerbations. Contributing comorbidities should be

evaluated and treated. Not all patients achieve control of dyspnea or exacerbations despite optimal available pharmacotherapy.

Some examples of agents used in the treatment of COPD:

Agents used in the treatment of COPD (not a complete list)		
	Generic name	**Sample brand names**
Short-acting beta agonists (SABAs)	Albuterol*	ProAir Digihaler, ProAir RespiClick, Proventil HFA, Ventolin HFA
	Levalbuterol*	Xopenex HFA
Short-acting muscarinic antagonist (SAMA)	Ipratropium	Atrovent HFA
SABA-SAMA combinations	Albuterol * plus ipratropium	Combivent Respimat
Long-acting beta agonists (LABAs)	Arformoterol	Brovana
	Formoterol	Perforomist
	Olodaterol	Striverdi Respimat
	Salmeterol	Serevent Diskus
Long-acting muscarinic antagonists (LAMAs)	Aclidinium	Tudorza Pressair
	Revefenacin	Yupelri
	Tiotropium	Spiriva HandiHaler
		Spiriva Respimat
	Umeclidinium	Incruse Ellipta
Steroid (ICS)-LABA combinations	Budesonide plus formoterol	Breyna, Symbicort
	Fluticasone propionate plus salmeterol	Advair Diskus, AirDuo Digihaler, AirDuoRespiClick, Wixela Inhub
		Advair HFA
	Fluticasone furoate plus vilanterol	Breo Ellipta
	Mometasone plus formoterol	Dulera
LAMA-LABA combinations	Aclidinium plus formoterol	Duaklir Pressair
	Glycopyrrolate plus formoterol	Bevespi Aerosphere
	Tiotropium plus olodaterol	Stiolto Respimat
	Umeclidinium plus vilanterol	Anoro Ellipta
ICS-LAMA-LABA combinations	Budesonide, glycopyrrolate, plus formoterol	Breztri Aerosphere
	Fluticasone furoate, umeclidinium, plus vilanterol	Trelegy Ellipta

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Resources:

Ohtuvayre (ensifentrine) inhalation oral suspension product information, revised by Verona Pharma, Inc. 06-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 25, 2024.

Han MK, Dransfield MT. Stable COPD: Initial pharmacologic management. In: UpToDate, Stoller JK, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated May 09, 2024. Accessed July 25, 2024.

Han MK, Dransfield MT. Stable COPD: Follow-up pharmacologic management. In: UpToDate, Stoller JK, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated July 12, 2024. Accessed July 25, 2024.

Stoller JK. COPD exacerbations: Clinical manifestations and evaluation. In: UpToDate, Barnes PJ, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated June 27, 2024. Accessed July 25, 2024.

Stoller JK. COPD exacerbations: Management. In: UpToDate, Barnes PJ, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated July 12, 2024. Accessed July 25, 2024.

Han MK, Dransfield MT. Management of refractory chronic obstructive pulmonary disease. In: UpToDate, Stoller JK, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated July 12, 2024. Accessed July 25, 2024.

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 Aug 15; 208(4); 406–416. Accessed July 25, 2024.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04535986: A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine Over 24 Weeks (With a 48-week Safety Subset) in Subjects With Moderate to Severe COPD. Available from: http://clinicaltrials.gov. Last update posted November 13, 2011. Last verified November 2011. Accessed July 25, 2024.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT04542057: A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine Over 24 Weeks in Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease. Available from: http://clinicaltrials.gov. Last update posted October 02, 2023. Last verified October 2023. Accessed July 25, 2024.

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, July 16, 2024. https://icer.org/assessment/copd-2024/. Accessed July 27, 2024.