BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

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/or 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.

Medical Necessity Requirements for OHTUVAYRE (ensifentrine)

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Pulmonologist or in consultation with a Pulmonologist

Indication
- Chronic obstructive pulmonary disease (COPD) for maintenance treatment

Age Requirement
- 18 years or older

ORIGINAL EFFECTIVE DATE: 08/15/2024 | ARCHIVE DATE: | LAST REVIEW DATE: 08/21/2025 | LAST CRITERIA REVISION DATE: 08/21/2025

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Baseline Clinical Evaluation

- Modified Medical Research Council dyspnea scale score greater than or equal to 2 or COPD Assessment Test (CAT) score greater than or equal to 10
- Pre and post albuterol/salbutamol FEV1/FVC ratio less than 0.70
- 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)
- Currently on **BOTH** of the following treatments for COPD:
  - LAMA and LABA dual bronchodilator therapy
  - LAMA, LABA, and ICS triple bronchodilator therapy
- Will be used as an add on therapy for COPD

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No concomitant use with oral phosphodiesterase 4 inhibitor Daliresp (roflumilast)
- Not used for acute symptoms of bronchospasm or as rescue therapy

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (include dyspnea scale score, COPD Assessment Test score, and forced expiratory volume in one second/forced vital capacity ratio)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in or is in consultation with a Pulmonologist

Clinical Response

- **ALL** the following:
  - Significant improvement from baseline in FEV1
  - Reduction in the number of moderate or severe exacerbations
  - Reduction in daily rescue medication use

- Delay in the time to next moderate or severe exacerbation
- Improvements in persistent shortness of breath, sputum production, and cough

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No significant paradoxical bronchospasm from Ohtuvayre use
- No concomitant use with oral phosphodiesterase 4 inhibitor Daliresp (roflumilast)
- Not used for acute symptoms of bronchospasm or as rescue therapy

Additional Requirements:

- Will be used as an add on therapy for COPD

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use from above criteria

Continuation Therapy Criteria Approval Duration:

- 12 months OR end of plan year

Criteria for Off-Label Use Requests:

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.

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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 I have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 meters of after a few minutes on level ground
4	I am too breathless to leave the house, or I am breathless when dressing or undressing

COPD Assessment Test (CAT)

	Circle the number that best describes you	
I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucous) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucous)
My chest does not feel tight at all	0 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	0 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	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 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	▪ Add LAMA (preferred) or LABA ▪ Continue current therapy is reasonable in those with minimal symptoms
• 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$^{\Delta}$
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-LABA
• LAMA or LABA monotherapy	▪ Change to LAMA-LABA
• LABA-ICS	▪ LAMA-LABA-ICS ▪ LAMA-LABA if lack response to or adverse effects from ICS
• LAMA-LABA	▪ Trial of LAMA-LABA-ICS, in patients with blood eosinophils ≥100 cells/microL or features of asthma◊ ▪ Add-on ensifentrine ▪ Additional interventions may include low-dose theophylline, repeat pulmonary rehabilitation, and nonpharmacologic therapies§
• LAMA-LABA + ensifentrine ± ICS	▪ Continue maximal inhaled therapies ▪ Trial of LAMA-LABA-ICS, in patients with blood eosinophils ≥100 cells/microL or features of concomitant asthma◊ ▪ Stop ICS, if lack of response, or adverse effect to ICSΔ ▪ Additional interventions may include low-dose theophylline, repeat pulmonary rehabilitation, and nonpharmacologic therapies for COPD§
+/– 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-LABA
• LAMA or LABA monotherapy	▪ LAMA-LABA, if blood eosinophil count <300/microL◊ Or ▪ LAMA-LABA-ICS, if blood eosinophil count ≥300/microL◊ or hospitalization for COPD exacerbation Or ▪ LABA-ICS, if blood eosinophil count ≥100/microL◊ **and** LAMA contraindicated
• LAMA-LABA	▪ LAMA-LABA-ICS, if blood eosinophil count ≥100/microL◊ Or ▪ Add ensifentrine (preferred), or roflumilast‡ or azithromycin†, if blood eosinophil count <100/microL¥
• LABA-ICS	▪ LAMA-LABA-ICS Or ▪ LAMA-LABA if adverse effects from ICSΔ
• LAMA-LABA-ICS	▪ Continue LAMA-LABA-ICS ▪ Add ensifentrine (preferred), or systemic therapies (roflumilast‡, azithromycin†, or dupilumab◊◊) ▪ Stop ICS if adverse effects of ICSΔ
• LAMA-LABA & ensifentrine ±ICS	▪ Continue maximal inhaled therapies ▪ Add roflumilast‡ or azithromycin† or dupilumab◊◊ ▪ Stop ICS if 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).	

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¶ 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.
◊◊ Dupilumab therapy is appropriate only for patients with peripheral eosinophilia (=300 cells/microL) or concomitant severe asthma.
§ 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

Resources:

Ohtuvayre (ensifentrine) inhalation oral suspension product information, revised by Verona Pharma, Inc. 06-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 14, 2025.

Han MK, Dransfield MT. Stable COPD: Initial pharmacologic management. In: UpToDate, Stoller JK, Hatipoglu U, Hussain Z, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated June 23, 2025. Accessed June 30, 2025.

Han MK, Dransfield MT. Stable COPD: Follow-up pharmacologic management. In: UpToDate, Stoller JK, Hussain Z, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated June 16, 2025. Accessed June 30, 2025.

Stoller JK, Hatipoglu U. COPD exacerbations: Clinical manifestations and evaluation. In: UpToDate, Barnes PJ, Li H, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated May 12, 2025. Accessed June 30, 2025.

Stoller JK, Hatipoglu U. COPD exacerbations: Management. In: UpToDate, Barnes PJ, Li H, Dieffenbach P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated May 14, 2025. Accessed June 30, 2025.

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Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025. Available from: http://goldcopd.org. Accessed June 30, 2025.

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. Re-evaluated June 30, 2025.

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. Re-evaluated June 30, 2025.

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. Re-evaluated June 30, 2025.

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. Re-evaluated June 30, 2025.