Ensifentrine Inhalation Suspension (OHTUVAYRE)
Criteria for Use
January 2025
VA Pharmacy Benefits Management Services and National Formulary Committee

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National Formulary Committee Monograph on this drug at the *PBM INTRAnet* site for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive ensifentrine.

- ☐ Diagnosis of asthma
- ☐ Treatment of acute bronchospasm or an acute exacerbation of chronic obstructive pulmonary disease (COPD)
- ☐ History of depression (e.g., major depressive disorder [MDD]), suicidal thoughts or behaviors, unless determined, in consultation with a mental health specialist or primary care provider, that ensifentrine can be used ^1

1. Other psychiatric adverse events reported with ensifentrine include insomnia and anxiety. Use with caution in patients with insomnia and anxiety and, although not part of the labeling, in patients with other mental health disorders (e.g., psychotic disorder, bipolar disorder, post-traumatic stress disorder (PTSD), etc.), especially if not fully controlled. Discussion with mental health provider may be appropriate.

Use with caution in patients with moderate to severe hepatic impairment as exposure to ensifentrine may increase up to 2.3-fold.

Inclusion Criteria

All of the following criteria must be met.

- ☐ Provider is a VA or VA Community Care pulmonologist or designated expert.
- ☐ Moderate to severe COPD (e.g., post-bronchodilator FEV1 30-70% predicted and FEV1/FVC <0.7, confirmed by pulmonary function testing). FEV: Forced expiratory volume; FVC: Forced vital capacity
- ☐ Receiving maintenance bronchodilator therapy with a long-acting beta-agonist (LABA) AND a long-acting anticholinergic (LAMA) AND an inhaled corticosteroid (unless inhaled corticosteroid is contraindicated) for at least 3 months.
- ☐ Had at least 2 moderate COPD exacerbations (requiring systemic steroids and/or antibiotics) or at least 1 severe COPD exacerbation (requiring hospitalization) in the previous 12 months.
- ☐ Inadequate symptom control (e.g., dyspnea score of at least 2 on Medical Research Council dyspnea scale, etc.) ^2
- ☐ Patient is unable to tolerate or had an inadequate response to roflumilast and/or azithromycin after therapeutic trial (e.g., continued exacerbations after at least 6 months) or is clinically not appropriate for either agent (e.g., risks outweigh benefits). ^3-5
- ☐ Adherent to COPD medications as evidenced by a review of prescription refill history.
- ☐ Patient has demonstrated correct inhaler technique (documented in medical record) ^6
- ☐ Potential for psychiatric events with ensifentrine such as mood changes, depression, anxiety and suicidal thoughts and/or behaviors have been discussed with the patient and documented in medical record.

2. https://www.pcrs-uk.org/sites/default/files/resources/MRC-Score.pdf
3. Roflumilast can reduce exacerbations in patients with FEV_1 <50% predicted and chronic bronchitis. Gastrointestinal events can be minimized with titration. Psychiatric effects including insomnia, anxiety, depression and suicidal thoughts may occur and patients should be informed. Weigh the benefit/risk in patients with a history of depression and/or suicidal thoughts or behavior. Combination with strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, etc.)

is not recommended. Concomitant use with CYP3A4 and/or CYP1A2 inhibitors may increase risk for adverse events. Do not use in patients with moderate to severe liver impairment (e.g., Child-Pugh B or C).

4. Azithromycin can reduce exacerbations in patients with FEV_1 <50% predicted and an exacerbation in the past year. Adverse events include prolonged QTc and hearing loss. Weigh benefit/risk in patients receiving multiple QT prolonging drugs, baseline hearing loss and concern for atypical mycobacterial infection.
5. A trial of both agents is not required, if not clinically appropriate.
6. Proper use of the inhaled device should be confirmed. If the patient is unable to use their inhaled device properly, consider change to an alternative device (dry powder inhaler (DPI), soft mist inhaler (SMI), metered dose inhaler (MDI)). If a switch is made, reassess, and confirm ability to use device properly.

Additional guidance:

Patient is non-smoking or, if not, he/she is enrolled in a quit smoking program or on medications to assist with smoking cessation. Current smokers may be considered if unable or refuse to quit.

Additional Inclusion Criteria

All of the following criteria must be met.

☐ For patients who can become pregnant: Counseling provided on potential risks vs benefits of treatment and the use of effective contraception during therapy.

Supplemental Information

- The Global Initiative for Chronic Obstructive Lung Disease, or GOLD, guidelines recommend considering roflumilast or azithromycin in patients that are on dual (eosinophils <100 cells/microliter) or triple inhaler therapy (eosinophils >100 cells/microliter) and continue to have exacerbations despite adherence with inhaled therapy and confirmed ability to use inhalers properly. Despite general guidance for use (e.g., roflumilast in patients with FEV1 <50% prediction and with chronic bronchitis or azithromycin, preferentially in former smokers), there is no clearer guidance directing the optimal choice between the two agents. There is an ongoing multicenter, noninferiority, comparative effectiveness study (RELIANCE) comparing azithromycin (250 mg daily, 500 mg three times weekly or alternate regimen) to roflumilast (500 mg daily or alternate regimen) in patients with COPD and chronic bronchitis who were hospitalized in the past year. The study is estimated to be completed in 2026.
- For patients with recurrent exacerbations despite maximized inhaled therapy, UpToDate suggests roflumilast, azithromycin or dupilumab as options. The choice between the three agents is largely based upon patient and disease characteristics from populations studied in clinical trials. For example, eosinophilic phenotype is required for dupilumab, presence of chronic bronchitis and FEV1 <50% predicted for roflumilast and more broadly for azithromycin but preferentially former smokers. Additionally, potential for adverse events (ADE) should also be considered in the selection including gastrointestinal ADE for roflumilast, long corrected QT interval (QTc) and hearing loss with azithromycin and injection site reactions for dupilumab. None of the three agents have been compared directly.

Prepared: December 2024. Contact: Cathy Kelley, PharmD, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)