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Drug Class Update with New Drug Evaluation: Miscellaneous Pulmonary Agents

Date of Review: December 2024

Date of Last Review: October 2020
Dates of Literature Search: 07/08/2020-09/05/2024
Brand Name (Manufacturer) Ohtuvayre™ (Verona Pharma)
Dossier Received: yes

Generic Name: Ensifentrine

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this update is to review new literature published on the effectiveness and safety of miscellaneous pulmonary agents (montelukast, roflumilast, zafirlukast, zileuton) since the last Pharmacy and Therapeutics (P & T) Committee review of this class at the October 2020 meeting. In addition, evidence for the safety and efficacy of a new nebulized product, ensifentrine (OHTUVAYRE) and the expanded indication for dupilumab in adults with chronic obstructive pulmonary disease (COPD) will be evaluated.

Plain Language Summary:
- Asthma and COPD are lung conditions that make it hard to breathe. Asthma occurs in children and adults and is caused by lung airways that narrow, swell, and are blocked by mucus. COPD is caused by damage to the lungs from cigarette smoke or other air pollutants. COPD occurs mostly in people 40 years of age and older. For both conditions, inhaled medicine can improve symptoms and make it easier to breathe.
- Inhalers are the first step in asthma or COPD treatment. Several types of inhaled medicines help with symptoms of asthma or COPD. Quick relief (or short-acting inhalers) relax the airways to help people breathe easier when they are short of breath. Long-acting inhalers prevent shortness of breath, coughing and chest tightness over time. In many people with asthma and COPD, inhalers that combine 2 or 3 types of medicines help people breathe better than inhalers that contain only one type of medicine.
- Several medicines that are taken by mouth may be added to inhalers if people continue to have symptoms. These medicines are used to prevent worsening disease and should not be used for immediate relief of symptoms. Oral medicines include montelukast, zafirlukast and zileuton to reduce inflammation and prevent asthma attacks. Roflumilast to decreases the likelihood of a COPD flare-ups (exacerbations). Evidence shows that roflumilast may not improve COPD symptoms or quality of life.
- The Food and Drug Administration (FDA) approved a new medicine, ensifentrine, for adults with COPD in 2024. Ensifentrine is inhaled using a special device called a nebulizer device twice a day. It should not be used for immediate relief or trouble breathing during a COPD flare up. In clinical studies, ensifentrine was better than placebo (no medicine) in reducing COPD symptoms over 12 weeks. The most common side effects of ensifentrine were back pain, high blood pressure, urinary tract infections, and diarrhea. An increase in mental health changes including thoughts of suicide was also noticed in clinical trials.

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- The FDA also approved dupilumab for adults with COPD who are not controlled with triple inhaler therapy. Dupilumab is already approved to use in certain patients with asthma. In clinical studies, dupilumab was better than placebo at decreasing how often people had COPD flare-ups.
- Oregon Health Plan will pay for montelukast without requiring prior authorization. Providers must explain to the Oregon Health Authority (OHA) why someone needs zafirlukast, zileuton or roflumilast before the Oregon Health Plan will pay for it. This process is called prior authorization. The Drug Use Research & Management Program recommends providers explain to the OHA why someone needs ensifentrine or dupilumab before the Oregon Health Plan will pay for it.

Research Questions:

1. What is the efficacy of the miscellaneous pulmonary agents (montelukast, roflumilast, zafirlukast, zileuton) in the treatment of asthma or COPD?
2. What are the harms of the miscellaneous pulmonary agents in the treatment of asthma or COPD?
3. Are there subgroups of patients (i.e., groups defined by demographics, disease severity, comorbidities) for which the oral miscellaneous pulmonary agents are better tolerated or more effective than other agents in this class?
4. What is the evidence for the safety and efficacy of ensifentrine, a recently approved inhaled nebulizer product for treatment of COPD?
5. What is the evidence for the safety and efficacy of dupilumab, which recently received the expanded indication as an add-on maintenance treatment of adults with inadequately controlled COPD?

Conclusions:

- No new high-quality evidence was identified to compare the safety and efficacy of montelukast, roflumilast, zafirlukast, and zileuton in people with asthma or COPD.
- No new evidence was identified to evaluate if there are subgroups of patients for which the oral miscellaneous pulmonary agents are better tolerated or more effective than other agents in this class.
- The Global Initiative for Asthma (GINA) report was updated in 2024. Recommendations for when to use leukotriene receptor antagonists (LTRAs) in treatment of asthma remain unchanged. Since LTRAs are less effective than inhaled corticosteroids (ICS), particularly for exacerbations (high-quality evidence), they are recommended as alternatives to preferred inhaler therapy.[1] Before prescribing montelukast, GINA advises that clinicians assess the benefits and risks and counsel patients or their parents/caregivers about the risk of neuropsychiatric events.[1]
- In June 2024, ensifentrine, a dual phosphodiesterase (PDE)-3 and PDE-4 inhibitor, received FDA-approval for maintenance treatment of COPD in adults at a dose of 3 mg by inhaled nebulizer twice daily.[2] The efficacy of ensifentrine was evaluated in 2 phase 3 trials (ENHANCE-1 and ENHANCE-2).[3] Patients enrolled in the 2 randomized controlled trials (RCTs) were aged 40 to 80 years, with moderate to severe COPD, and a smoking history $\geq$ 10 pack-years.[3] In both trials, patients were permitted to receive concurrent long-acting muscarinic antagonist (LAMA) or long-acting beta agonist (LABA) inhaler therapy with or without an ICS.[4] The primary endpoint was impact on bronchodilation from baseline to week 12 as assessed by the change in forced expiratory volume in one second (FEV_1) area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$).[3] Moderate-quality evidence shows that compared with placebo, ensifentrine improved the least squares mean (LSM) change in FEV_1 $AUC_{0\text{-}12h}$ from baseline to week 12 in both RCTs.[3] The minimal clinically important difference (MCID) in FEV_1 values for COPD changes has not been clearly defined, but research in COPD patients suggests that minimally important FEV_1 changes range from 100 to 140 mL.[5]

Trial	Placebo (mL)	Ensifentrine (mL)	Difference (mL)
ENHANCE-1	-26	61	87 (95% CI 55 to 119)
ENHANCE-2	-46	48	94 (95% CI 65 to 124)

- Adverse reactions that occurred in at least 1% of people treated with ensifentrine which were more common than placebo included back pain, hypertension, urinary tract infection, and diarrhea (**Table 4**).[3] Treatment with ensifentrine is associated with an increase of psychiatric adverse reactions.[2] Before initiating treatment with ensifentrine, healthcare providers should carefully weigh the risk and benefits of treatment in patients with a history of depression and/or suicidal thoughts or behavior, and re-evaluate the risks and benefits of continuing treatment if such events occur.[2] The oral PDE-4 inhibitor, roflumilast also carries this warning in the prescribing information.[6]
- Ensifentrine was not studied with all possible combinations of medications that are currently recommended to treat COPD, as patients receiving concurrent LAMA/LABA inhaler or triple therapy (LAMA/LABA/ICS) were excluded from enrollment. Current treatment guidelines recommend LABA/LAMA as first-line therapy for patients with moderate COPD and the exclusion of patients on LABA/LAMA may limit generalizability of the results.[7] In addition, the proportion of people identifying as Black was limited to 3.3% of the enrolled population and only 2.8% of patients identified as Hispanic or Latino (where race and ethnicity were recorded).[7] While these percentages are similar to that of the published United States (US) epidemiologic data, COPD may be underreported in these groups within the US population,[8] and the limitations in racial and ethnic diversity may impact generalizability of the results.[7]
- There is no available data on ensifentrine use in pregnant or lactating women to evaluate for drug-associated risk of adverse maternal or fetal outcomes.[2] The safety and effectiveness of ensifentrine have not been established in pediatric patients.[2] Finally, head-to-head clinical trials with ensifentrine and other COPD maintenance medications have not been conducted. Additional data is needed to assess the impact of ensifentrine on reducing COPD exacerbations and hospitalizations and improving quality of life.
- In September 2024, dupilumab (DUPIXENT) received an expanded FDA-approved indication as an add-on maintenance treatment for adults with inadequately controlled COPD.[9] The FDA based the approval on pooled data from 2 RCTs (BOREAS and NOTUS) conducted in adults with COPD who were receiving triple inhaler therapy (LAMA/LABA/ICS).[10,11] In the BOREAS trial, 939 patients with COPD who had a blood eosinophil count of at least 300 cells/µL and an elevated exacerbation risk despite the use of standard triple therapy underwent randomization to dupilumab 300 mg or placebo subcutaneously (SC) every 2 weeks.[10] The primary end point was the annualized rate of moderate or severe exacerbations of COPD at 52 weeks.[10] The annualized rate of moderate or severe exacerbations was 0.78 with dupilumab and 1.10 with placebo (rate ratio, 0.70; 95% CI, 0.58 to 0.86; P<0.001).[10] The NOTUS trial enrolled 935 patients with similar characteristics to the BOREA trial and used the same primary endpoint.[11] At 52 weeks, the annualized rate of moderate or severe exacerbations was 0.86 with dupilumab and 1.30 with placebo (rate ratio, 0.66; 95% CI, 0.54 to 0.82; P<0.001).[11] In both trials, the incidence of adverse events (AEs) was similar in between dupilumab and placebo and consistent with the established profile of dupilumab.[10,11]

Recommendations:

- Review of clinical evidence does not warrant changes in the preferred drug list (PDL) for miscellaneous pulmonary agents.
- Revise prior authorization (PA) criteria for dupilumab to include use in adults with inadequately controlled COPD on triple inhaler therapy (**Appendix 5**).
- Maintain ensifentrine as non-preferred on the PDL with specific PA criteria to ensure patient is using guideline directed therapy prior to adding ensifentrine to therapeutic regimen (**Appendix 5**).
- Revise roflumilast PA criteria to specify the criteria refer to oral roflumilast tablets and add renewal criteria.

Summary of Prior Reviews and Current Policy

- Literature for asthma and COPD maintenance medications was last evaluated in October 2020. At that meeting the P & T Committee approved the recommendation to update prior authorization (PA) roflumilast criteria with the clinical definition of severe and very severe COPD (**Appendix 5**). The PDL status for the oral miscellaneous pulmonary agents is provided in **Appendix 1.**

- At the February 2024 meeting, the P & T Committee reviewed inhalers for COPD and asthma. After review of the evidence, the Committee agreed to revise PA criteria for inhaled therapies used to managed asthma and COPD to align with updated guidance from the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report. The 2023 GOLD guidance recommends a combination long-acting muscarinic antagonist (LAMA) and long-acting beta agonist (LABA) inhaler as initial therapy for two COPD patient groups (B and E, see **Table 1**). The PA criteria for combination LAMA-LABA and LAMA-LABA-inhaled corticosteroid (ICS) inhalers was modified to remove PA from preferred products.
- Most of the utilization for oral pulmonary drugs is for montelukast which is the only preferred oral product (99% of claims).

Background:

Asthma

Asthma is a heterogeneous disease, characterized by chronic, reversible, airway inflammation which results in bronchial hyper-responsiveness. It is defined in the 2023 Global Initiative for Asthma (GINA) guidance by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough.[12] Symptom severity can vary over time and be associated with changes in bronchial expiratory volume.[13] In 2019, the Centers for Disease Control and Prevention (CDC) estimated that 25 million Americans, including 5 million children had asthma.[14] In the US, asthma is more than twice as common among children identifying as Black compared to children identifying as White (13.5% and 6.4% respectively).[14]

Diagnosis of asthma is confirmed by spirometry (improvement in FEV_1 > 200 mL or ≥ 12% from baseline after short-acting beta agonist [SABA] use), which demonstrates airway obstruction that is at least partially reversible.[12] The GINA guidelines base initial pharmacotherapy on assessment of the frequency and severity of asthma symptoms.[12] For Step 1 and 2 therapy, the 2023 GINA guideline recommends use of a combination low-dose inhaled corticosteroid (ICS) and the fast-acting LABA such as formoterol be taken as needed for symptom relief.[12] For moderate asthma (Step 3), the preferred maintenance therapy is a combination low-dose ICS and LABA inhaler.[12] For severe asthma, the preferred treatments are medium (Step 4) or high (Step 5) doses of an ICS in combination with a LABA.[12]

Three LTRAs, montelukast, zafirlukast, and zileuton, are FDA-approved for the treatment of asthma in adults and children. The LTRAs exert anti-inflammatory effects in addition to their bronchodilating actions.[15] In general, the magnitude of anti-inflammatory effects associated with LTRAs is less than ICS products.[16] In the GINA guidance, LTRAs are recommended as alternative controller options because they have less evidence for safety and efficacy compared with inhaler therapy.[12] Daily administration of LTRAs may be added in Steps 2, 3, or 4 to the recommended inhaler treatment for that step.[12]

In March 2020, the FDA placed a boxed warning on montelukast, advising that all patients should be warned about potential behavior and mood-related changes when starting this medication.[17] Providers should consider the potential risks and benefits of montelukast, particularly when the patient has mild asthma or allergic rhinitis or has a history of psychiatric illness; and patients should be monitored for neuropsychiatric symptoms.[17] This warning is based on postmarketing surveillance of neuropsychiatric events (e.g., agitation, depression, insomnia, suicidal thoughts and actions) among patients taking montelukast.[17] It should be noted that depression and suicidality are more common in patients with asthma than in the general population.[18]

Zileuton is associated with more frequent adverse effects than montelukast and zafirlukast, including liver inflammation and drug interactions. Zileuton should be avoided in patients with liver disease or substantial alcohol consumption.[19] The manufacturer recommends monitoring serum alanine aminotransferase (ALT) monthly for the first 3 months of therapy, then every 2 to 3 months for the rest of the first year, and periodically thereafter.[19] Zileuton should be discontinued if ALT is ≥ 3 times normal, which occurred in 2% of patients treated with zileuton for at least one year, compared with 0.2 percent of placebo recipients.[19] Drug

interactions are possible as zileuton inhibits cytochrome CYP1A2 and has a mild interaction with CYP2C9, and CYP3A4.[19] Co-administration of zileuton with theophylline, warfarin, or propranolol may increase serum concentrations of these agents and medication doses should be adjusted as needed.[19]

Systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, has been reported in steroid-dependent asthmatics treated with LTRAs.[20] In most instances, symptoms have occurred following oral glucocorticoid tapers , suggesting that underlying complication may be unmasked by glucocorticoid withdrawal, rather than being caused by the LTRAs themselves.[20] Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients.[21] A causal association between LTRAs and these underlying conditions has not been established.[21]

Chronic Obstructive Pulmonary Disease

The 2023 GOLD report updated the definition of COPD as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction".[5] The most common cause of COPD is airway irritation, usually from cigarette smoking, although exposure to other environmental pollutants can contribute to the condition.[5] COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic therapy.[22] Current estimates suggest that approximately 10 percent of individuals aged 40 years or older have COPD, although the prevalence varies between countries and increases with age.[23-25] COPD is one of the leading causes of death among adults in the United States, resulting in over 140,000 deaths annually.[26]

Important outcomes to access the effectiveness of COPD therapies include changes in lung function, quality of life (QoL), dyspnea, exacerbation rate and/or severity, and AEs. The most common surrogate outcome used in studies to determine therapy effectiveness is post-bronchodilator FEV_1.[27] The minimal clinically important difference (MCID) in FEV_1 values for COPD changes have not been clearly defined, but research in COPD patients suggest that minimally important FEV_1 changes range from 100 to 140 mL.[5] The GOLD guidance recommends assessment of COPD symptoms using the modified Medical Research Council (mMRC) dyspnea questionnaire.[5,28] This 4-point, patient-reported questionnaire assesses extent of breathlessness on a scale of 0 (breathlessness only with exercise) to 4 (breathlessness when dressing).[5] A score of 2 or greater on the mMRC indicates symptomatic COPD. The mMRC relates well to other health measures and predicts future mortality risk.[29] The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on QoL with scores ranging from 0 to 100. Higher scores on the SGRQ indicate more QoL limitations.[30] The MCID on the SGRQ is an improvement of 4 points.[3] The SGRQ is an important research tool, but is too complex to use in routine clinical practice.[29] The COPD Assessment Test (CAT) is a shorter health assessment tool that is suitable for use in the clinic.[5,31] The 8-item questionnaire ranges in score from 0 (best) to 40 (worst) points and correlates very closely with the SGRQ.[5] A score of 10 on the CAT should be used as the threshold for considering regular treatment of COPD symptoms.[29] The Evaluating Respiratory Symptoms (E-RS) is a patient-reported diary that assesses respiratory symptoms in stable COPD.[32] This tool was developed to quantify respiratory symptoms in clinical trials.[32] The E-RS tool consists of 11 questions, with 3 sub-domains of: breathlessness, cough and sputum, and chest symptoms.[32] The E-RS total score is derived as the sum of the raw scores of the 11 items ranging from 0 to 40.[32] Higher scores indicate severe respiratory symptoms.[32] The MCID on the E-RS is a change of 2 points.[3] The E-RS tool has been recognized by the FDA as a valid and reliable measure of respiratory symptom severity for use in clinical trials of COPD.[33]

The diagnosis and management of COPD are based on spirometry post-bronchodilation results which indicate airflow obstruction (i.e., FEV_1/forced vital capacity [FVC]) <0.70), symptom severity, risk of exacerbations and comorbidities.[5] Treatment of COPD is aimed at symptom relief, improving exercise tolerance, preventing disease progression, and treating and preventing exacerbations. The GOLD report uses the core metrics of dyspnea severity and frequency of

exacerbations to categorize patients for pharmacologic management.[29] Initial management uses these metrics to divide patients into GOLD "ABE" groups for choice of initial therapy (**Table 1**).[29]

Table 1. 2023 GOLD COPD Classification (Post bronchodilator FEV_1/FCV <0.7) [5]

Classification	Symptoms	Exacerbations
GOLD Category A	mMRC 0-1 or CAT <10	History of 0-1 moderate to severe exacerbations (not leading to hospitalization) per year
GOLD Category B	mMRC ≥2 or CAT ≥10	
GOLD Category E	mMRC ≥2 or CAT ≥10	History of ≥2 moderate/severe exacerbations or ≥1 exacerbation (leading to hospitalization) per year

Abbreviations: CAT = COPD Assessment Test; COPD = Chronic Obstructive Lung Disease; FEV_1 = forced expiratory volume in 1 second; FCV = forced vital capacity; GOLD = Global Initiative for COPD; mMRC = modified Medical Research Council questionnaire

Inhalers that are FDA-approved to manage COPD include SABAs, short-acting muscarinic antagonists (SAMAs), LABAs, long-acting muscarinic antagonists (LAMAs) and combination therapy with an inhaled corticosteroid (ICS). The COPD classification tool is the foundation for initiation of COPD inhaler treatment.[5] **Table 2** summarizes the 2023 GOLD pharmacotherapy guidance for initial treatment of COPD.

Table 2. GOLD 2023 Initial Pharmacologic Treatment Recommendations[5]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization per year	Group E LABA + LAMA* *Consider LABA + LAMA + ICS if blood eosinophils ≥ 300 cells/µL*	
0 or 1 moderate exacerbations per year (not leading to hospital admission)	Group A Bronchodilator	Group B LABA + LAMA*
	mMRC 0-1; CAT <10	mMRC ≥ 2; CAT ≥ 10

***Single inhaler therapy may be more convenient and effective than multiple inhalers*

Abbreviations: CAT = COPD Assessment Tool; eos = eosinophils; ICS = inhaled corticosteroid; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; mMRC = modified Medical Research Council Dyspnea Questionnaire

Roflumilast, an oral phosphodiesterase (PDE)-4 inhibitor, is FDA-approved to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[6] Roflumilast does not have direct bronchodilator activity, so it should not be used to relieve acute bronchospasm.[6] Data show that roflumilast may have greater benefit in patients with a prior history of hospitalization for an acute COPD exacerbation.[5] There has been no study directly comparing roflumilast with an inhaled corticosteroid.[5] The 2023 GOLD guidance provides an algorithm for follow-up pharmacologic treatment where management is based on 2 key treatable traits: persistence of dyspnea and occurrence of exacerbations.[5] Roflumilast is included in this algorithm for COPD patients adequately treated with LABA-LAMA-ICS therapy, but continue to have yearly exacerbations, FEV_1 less than 50%, and chronic bronchitis.[5] The GOLD guidance recommends the use of roflumilast as add-on maintenance therapy to prevent exacerbations; it is not recommended for improvement in other COPD outcomes.[5]

Side effects are frequently experienced in patients who take roflumilast. In 2017, the FDA added a warning that roflumilast may be associated with an increase in adverse psychiatric reactions and should be used with caution in patients with a history of depression and/or suicidal thoughts or behavior.[6] Other adverse effects include insomnia, diarrhea, nausea, vomiting, weight loss, and decreased appetite.[6] Adverse effects generally occur early during treatment, are reversible with treatment discontinuation, and diminish over time with continued treatment.[5] The manufacturer recommends starting low-dose roflumilast (250 mg once a day) for the first 4 weeks of treatment, although this is not an effective, therapeutic dose. Starting treatment at 250 mg once daily and increasing to the therapeutic dose of 500 mg once daily after 4 weeks, may reduce the rate of treatment discontinuation in some patients.[6]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Oregon Mental Health Clinical Advisory Group (MHCAG), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 7 systematic reviews were excluded due to poor quality,[34-38] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[39,40] or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:
Global Initiative for Asthma
The Global Initiative for Asthma (GINA) report was updated in 2024. Recommendations for the use of LTRAs in asthma management remain unchanged. Since LTRAs are less effective than ICS, particularly for exacerbations (high-quality evidence), they are recommended as alternatives to preferred inhaler therapy.[1] However, the boxed warning issued in 2020 by the FDA for neuropsychiatric events, has been incorporated into montelukast recommendations. Before prescribing montelukast, clinicians should assess the benefits and risks and counsel patients or their parents/caregivers about the risk of neuropsychiatric events.[1]

New Indications:
In September 2024, dupilumab received an expanded FDA-approved indication as an add-on maintenance treatment of adults with inadequately controlled COPD.[9] The FDA based the approval on pooled data from two phase 3 RCTs (BOREAS and NOTUS) which demonstrated that dupilumab 300 mg SC every 2 weeks improved lung function and reduced COPD exacerbations in current or former smokers with moderate to severe COPD and type 2 inflammation (blood eosinophil count ≥ 300 cells/μL) after 52 weeks.[10,11] Trial enrollment required an exacerbation history of at least 2 moderate or 1 severe exacerbation(s) in the previous year despite receiving maintenance triple inhaler therapy (ICS/LABA/LAMA) and symptoms of chronic productive cough for at least 3 months in the past

year.[9] The primary end point was the annualized rate of moderate or severe exacerbations of COPD.[10] Exacerbations of COPD were defined as clinically significant worsening of COPD symptoms including increases in dyspnea, wheezing, cough, sputum volume, and/or increase in sputum purulence. Exacerbation severity was further defined as moderate if treatment with systemic corticosteroids and/or antibiotics was required, or severe if they resulted in hospitalization or observation for over 24 hours in an emergency department or urgent care facility.[9] Key secondary and other end points were the change in from baseline over 12 and 24 weeks in the FEV_1 and in the scores on the SGRQ (range, 0 to 100, with lower scores indicating a better quality of life).[10] Both trials were funded and designed by the manufacturers (Sanofi and Regeneron Pharmaceuticals). In the BOREAS trial, a total of 939 patients aged 40 to 80 years, who were current or former smokers, underwent randomization to dupilumab or placebo.[10] This was a multi-center, international trial conducted at 275 sites in 24 countries over 52 weeks.[10] In this trial, 0.5% of enrolled patients were Black, 84% were White, 14% were Asian, and 0.7% were American Indian or Alaska Natives.[9] The mean number of moderate or severe COPD exacerbations in the previous year was 2.3.[9]

The annualized rate of moderate or severe exacerbations was 0.78 with dupilumab and 1.10 with placebo (rate ratio, 0.70; 95% CI, 0.58 to 0.86; p<0.001).[10] The prebronchodilator FEV_1 increased from baseline to week 12 by a least squares (LS) mean of 160 mL with dupilumab and 77 mL with placebo (LS mean difference, 83 ml; 95% CI, 42 to 125; P<0.001), a difference that was sustained through week 52.[10] At week 52, the SGRQ score had improved by an LS mean of −9.7 with dupilumab and −6.4 with placebo (LS mean difference, −3.4; 95% CI, −5.5 to −1.3; P=0.002).[10] This change was statistically significant, but did not meet the MCID of 4 points. The numbers of patients with AEs that led to discontinuation of dupilumab or placebo, serious AEs, and AEs that led to death were balanced in the two groups.[10] Limitations of the BOREAS trial included data collection during the coronavirus disease 2019 pandemic, which affected the conduct of clinical research and patient exposures and behaviors worldwide.[10] These factors may have contributed to challenges in recruitment and decreased frequencies of COPD exacerbations.[10] Despite recruitment efforts to ensure a representative population, patients who identified as Black were underrepresented.[10]

The NOTUS trial included 935 patients who were current or former smokers, aged 40 to 85 years from 329 sites in 29 countries.[11] Most of the enrolled patients were White (90%), 1.3% were Black, 1.1% were Asian, and 5% were American Indian or Alaska Natives.[9] The mean number of moderate or severe COPD exacerbations in the previous year was 2.1.[9] After 52 weeks, the annualized rate of moderate or severe exacerbations was 0.86 with dupilumab and 1.30 with placebo (rate ratio 0.66; 95% CI, 0.54 to 0.82; p<0.001).[11] The prebronchodilator FEV_1 increased from baseline to week 12 with dupilumab (LS mean change, 139 ml) as compared with placebo (LS mean change, 57 ml), with a LS mean difference at week 12 of 82 ml (95% CI 40 to 124; P<0.001) and at week 52 of 62 ml (95% CI 11 to 113; P=0.02).[11] At week 52, the decrease from baseline in SGRQ total score (indicating improvement) was -9.8 points in the dupilumab group and -6.4 points in the placebo group (LS mean difference, -3.4 points; 95% CI, -5.8 to -0.9).[11] This change was statistically significant but did not meet the MCID of 4 points. The incidence of adverse events was similar in the two groups and consistent with the established profile of dupilumab.[11]

This trial also has limitations. The sample size for the week-52 end points was reduced owing to the early primary analysis, which reduced the statistical power for some week-52 end points.[11] In addition, this trial was limited by the enrollment of a predominantly White population and other races were underrepresented.[11] Finally, the trial was conducted during the global Covid-19 pandemic, which led to disruptions in health care and changes in behaviors that, at times, led to decreased exposure to viral respiratory infections.[11] Although the trial included patients who were enrolled at a time when the interruptions and effects of Covid-19 were less pronounced (e.g., 2022 and 2023), the Covid-19 pandemic and related behavioral changes could affect the generalizability of the results.[11]

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Montelukast	Singular	2/2021	Warnings and Precautions	SINGULAIR contains aspartame, a source of phenylalanine. Phenylalanine can be harmful to patients with phenylketonuria (PKU). Each 4 mg and 5 mg chewable tablet contains 0.674 mg and 0.842 mg of phenylalanine, respectively. Before prescribing SINGULAIR to a patient with PKU, consider the combined daily amount of phenylalanine from all sources, including SINGULAIR.[21]

Randomized Controlled Trials:

A total of 28 citations were manually reviewed from the initial literature search. After further review, 28 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Ensifentrine (OHTUVAYRE)

Ensifentrine is a dual PDE3 and PDE4 inhibitor with bronchodilator and anti-inflammatory effects. Acting through regulation of cyclic adenosine monophosphate (cAMP), PDE3 increases airway smooth muscle tone, and PDE4 promotes inflammatory cell activation.[41,42] Ensifentrine is FDA-approved for maintenance treatment of COPD in adults at a dose of 3 mg by inhaled nebulizer twice daily.[2]

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The efficacy of ensifentrine was evaluated in 2 concomitant phase 3 trials (ENHANCE-1 and ENHANCE-2).[3] Both studies were double-blind, placebo-controlled, parallel-group RCTs conducted in adults with moderate to severe COPD (defined as postbronchodilator FEV_1/FVC ratio < 0.70 and post bronchodilator FEV_1 percent predicted > 30% and ≤70%) over 24 weeks.[3] After 24 weeks, the ENHANCE-1 trial enrolled a subset of patients into an additional 24 week safety analysis for a total study period of 48 weeks.[3] A total of 760 (ENHANCE-1) and 789 (ENHANCE-2) patients were randomized to either twice-daily ensifentrine or placebo after a 28-day run-in period to ensure stable background medication use.[3] Patients were stratified by trial duration (24 or 48 weeks for ENHANCE-1 only), background medication use (yes, no), and smoking status (current, former).[3]

Eligible patients were aged 40 to 80 years, with moderate to severe COPD and a smoking history of at least 10 pack-years.[3] Patients with asthma were excluded from enrollment. In ENHANCE-1, patients were a mean age of 65 years, 58% were male, 90% were White, 57% were current smokers, and 25% of patients reported COPD exacerbations within 15 months prior to the study.[3] Patients in ENHANCE-2 were a mean age of 65 years, 48% were male, 95% were White, 55% were current smokers, and 21% of patients reported COPD exacerbations within the 15 months prior to the study.[3] In both trials, patients were permitted to receive concurrent LAMA or LABA inhaler therapy with or without an ICS or received no long-acting maintenance therapy.[3] However, patients on LABA/LAMA or LABA/LAMA/ICS combination therapy were excluded from enrollment. Sixty-eight percent of patients in ENHANCE-1 received concomitant LAMA or LABA or

LABA/ICS therapy (30% taking concurrent LAMA, 18% taking concurrent LABA, and 20% taking concurrent LABA/ICS therapy).[2] Fifty-five percent of patients ENHANCE-2 received concomitant inhaler treatment (33% taking concurrent LAMA, 7% taking concurrent LABA, and 15% taking concurrent LABA/ICS therapy).[2] These trials were conducted between September 2020 and December 2022 before the GOLD guidelines were revised to recommend LABA/LAMA or LABA/LAMA/ICS combination therapy in patients with moderate to severe COPD.[3]

The objectives of the RCTs were to compare the effects of ensifentrine with placebo for changes in lung function, COPD symptoms, and quality of life.[3] Spirometry was conducted using centralized equipment and blinded central assessors.[3] Patients received an electronic diary at screening for recording daily rescue medication use, evaluating symptoms using the E-RS scale, and treatment adherence.[3] During clinic visits, the SGRQ was used to assess quality of life.[3] Additional details of both RCTs are provided in the comparative evidence table (**Table 6**).

The primary endpoint was impact on bronchodilation from baseline to week 12 as assessed by the change in FEV_1 area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$).[3] The average FEV_1 $AUC_{0–12\,h}$, was selected to assess bronchodilatory effects over 12 hours and was calculated as the AUC (pre-dose and 30 min and 1, 2, 4, 6, 8, and 12 h post-dose) using the trapezoidal method, divided by the 12 hours.[3] Secondary outcomes included change in peak FEV_1 and trough FEV_1 from baseline to week 12, change in COPD symptoms (E-RS) at week 24, and change in quality of life (SGRQ) at week 24.[3] Analyses were conducted utilizing the modified intention to treat (mITT) population, which included all patients randomized and dosed with medication or placebo.[3] Secondary endpoints were tested in a step-down sequential order approach to control type I error: 1) FEV_1 $AUC_{0–12h}$ (Week 12), 2) peak FEV_1 (Week 12), 3) E-RS total score (Week 24), 4) SGRQ total score (Week 24), and 5) morning trough FEV_1 (Week 12).[3] Data are presented as the LS mean change from baseline. Missing data were imputed using a multiple imputation approach with a missing at random assumption for continuous endpoints.[3]

Compared with placebo, ensifentrine improved the LS mean change in FEV_1 $AUC_{0\text{-}12h}$ from baseline to week 12 in both RCTs (ENHANCE-1, -26 vs. 61; difference = 87 ml; 95% CI 55 to 119 and in ENHANCE-2, -46 vs. 48; difference = 94 ml, 95% CI 65 to 124; both P<0.001).[3] Ensifentrine treatment demonstrated improvement in week 12 peak FEV_1 from baseline versus placebo (ENHANCE-1, 204 vs. 57; difference = 147 mL 95% CI 111 to 183; ENHANCE-2, 295 vs. 48; difference = 146 ml 95% CI 113 to 179; both $P < 0.001$).[3] In ENHANCE-1, ensifentrine treatment improved symptoms compared with placebo as assessed by the change in E-RS and SGRQ scores at week 24 (E-RS: -2.2 vs. -1.3; difference = −1.0; 95% CI −1.7 to −0.2; P=0.011 and SGRQ: -6.2 vs. -3.9; difference = −2.3; 95% CI −4.3 to −0.3; P=0.025).[3] The improvement MCID of 2 for E-RS and 4 for SGRQ did not meet clinical significance.[3] In ENHANCE-2, the changes between ensifentrine and placebo in E-RS and SGRQ were not statistically significant (E-RS: -2.1 vs. -1.5; difference = -0.6; 95% CI -1.4 to 0.2; P = 0.134) and SGRQ: -4.5 vs. -4.1; difference = -0.5; 95% CI -2.7 to 1.7; P = 0.669).[3] Trough FEV_1 was defined as the last FEV_1 value collected prior to the morning dose.[2] The mean morning trough FEV_1 improvement at week 12 relative to placebo was 35 mL (95% CI 14 to 68; P=0.041) and 49 mL (95% CI 19 to 80; p =0.002) in ENHANCE-1 and ENHANCE-2, respectively.[3] Due to the statistical hierarchy of outcome assessment, this outcome was statistically significant in ENHANCE-1 but not ENHANCE-2.[3]

Clinical Safety:
Adverse reactions that occurred at an incidence greater than or equal to 1% in ensifentrine and were more common than placebo in the pooled population from ENHANCE-1 and ENHANCE-2 included back pain, hypertension, urinary tract infection, and diarrhea (**Table 4**).[3] Rates of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs resulting in withdrawal or death were low in both trials and similar in ensifentrine- and placebo-treated patients.[3] The proportion of patients who discontinued treatment due to AEs was 7.6% for the ensifentrine-treated patients and 8.2% for placebo-treated patients.[3] In the 48-week cohort of ENHANCE-1, 369 patients were enrolled to be treated with 3 mg ensifentrine (N=280) or placebo (N=89) twice daily for 48 weeks.[2] The AEs reported in the 48-week cohort were consistent with those observed in the pooled 24-week safety population.[2]

Table 4. Adverse Reactions ≥ 1% with Ensifentrine Compared with Placebo In Pooled Data from ENHANCE-1 And ENHANCE-2 Over 24 Weeks[2]

Adverse Reaction	Ensifentrine N=975	Placebo N=574
Back Pain	18 (1.8%)	6 (1.0%)
Hypertension	17 (1.7%)	5 (0.9%)
Urinary Tract Infection	13 (1.3%)	6 (1.0%)
Diarrhea	10 (1.0%)	4 (0.7%)

Treatment with ensifentrine is associated with a slight increase in psychiatric adverse reactions.[2] Psychiatric events including suicide-related adverse reactions were reported in ENHANCE-1 and ENHANCE-2.[2] One patient who received ensifentrine in the pooled 24-week safety population experienced a suicide-related adverse reaction (suicide attempt).[2] The most commonly reported psychiatric adverse reactions in the pooled 24-week safety population were insomnia (6 patients [0.6%] ensifentrine 3 mg; 2 patients [0.3%] placebo), and anxiety (2 patients [0.2%] ensifentrine 3 mg; 1 patient [0.2%] placebo).[2] Depression-related reactions including depression, major depression, and adjustment disorder with depressed mood occurred in 4 patients [0.4%] receiving ensifentrine and no patients receiving placebo.[2] Before initiating treatment with ensifentrine, healthcare providers should carefully weigh the risk and benefits of treatment in patients with a history of depression and/or suicidal thoughts or behavior.[2] Healthcare providers should carefully evaluate the risks and benefits of continuing treatment with ensifentrine if such events occur.[2]

Trial Limitations:

Ensifentrine was not studied with all possible combinations of medications that are currently recommended to treat COPD, as patients receiving concurrent LAMA/LABA, or triple therapy (LAMA/LABA/ICS) were excluded from enrollment. Current treatment guidelines recommend combination LABA/LAMA as first-line therapy for patients with moderate COPD and the exclusion of patients on LABA/LAMA in the phase 3 trials may limit generalizability of the results and makes it difficult to evaluate the appropriate place of ensifentrine in COPD treatment.[7] In addition, the proportion of people identifying as Black was limited to 3.3% of the enrolled population and only 2.8% of patients were reported as Hispanic or Latino (where race and ethnicity were recorded).[7] While these percentages are similar to that of the published US epidemiologic data, COPD may be underreported in these groups within the US population,[8,43] and the limitations in racial and ethnic diversity may impact generalizability of the results.[7]

The primary endpoint for the two phase 3 RCTs was average change in FEV_1 $AUC_{0\text{-}12h}$ from baseline to Week 12. While the use of FEV1 $AUC_{0\text{-}12h}$ as the primary endpoint is considered reasonable, the FDA had concerns regarding using FEV_1 $AUC_{0\text{-}12h}$ as the ensifentrine treatment effect may be driven by a bronchodilatory response shortly after dosing with minimal or no effect at the end of the dosing interval.[7] Due to this concern, the FDA recommended using the morning trough FEV_1 as the primary endpoint in these studies to provide an assessment of the impact of the medication at the end of the dosing interval.[7] The investigators used trough FEV_1 as secondary endpoint.

This trial did not enrich for subjects with COPD who had frequent exacerbations and about 26% of people experienced an exacerbation within the 15 months before enrollment in the trial.[7] Patients with an exacerbation within 3 months prior to study enrollment were excluded. Compared to the average rate of COPD exacerbations within the general COPD population,[44] baseline exacerbations in the studied population appeared to be low.[7,44] Definitive conclusions regarding the impact of ensifentrine on reducing exacerbations are limited due to the exploratory nature of the exacerbation endpoint and small sample size within each subgroup.[7]

There is no available data on ensifentrine use in pregnant or lactating women to evaluate for drug-associated risk of adverse maternal or fetal outcomes.[2] The safety and effectiveness of ensifentrine have not been established in pediatric patients.[2] Finally, head-to-head clinical trials with ensifentrine and other COPD maintenance medications have not been conducted. There is no data comparing ensifentrine to current first-line treatment options for people with moderate to severe COPD (e.g., combination LABA/LAMA) and the role of ensifentrine as add-on therapy to current standard of care for COPD is unknown.

Look-alike / Sound-alike Error Risk Potential: No results reported

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) COPD symptoms (E-RS)
2) Quality of life (SGRQ)
3) COPD exacerbations
4) Hospitalizations
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in FEV_1 area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$) over 12 weeks

Table 5. Pharmacology and Pharmacokinetic Properties.[2]

Parameter	
Mechanism of Action	Dual PDE3 and PDE4 enzyme inhibitor
Oral Bioavailability	Time to maximum absorption: 0.6 to 1.5 hours
Distribution and Protein Binding	Healthy subjects: central Vd = 2700 L and peripheral Vd = 1820 L. In patients with COPD: central Vd = 8150 L and peripheral Vd = 5490 L. 90% protein bound
Elimination	Renal excretion < 0.3%, fecal excretion is the major route of elimination
Half-Life	10.6 to 12.6 hours
Metabolism	Primarily metabolized by CYP2C9 and to a lesser extent, CYP2D6

Abbreviations: COPD = chronic obstructive pulmonary disease; PDE = phosphodiesterase; L = liters; Vd = volume of distribution

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Anzueto A., et al[3]. ENHANCE-1 DB, MC, PC, PG phase 3 RCT Study Duration: 24 wks with an additional 24 wk extension for safety analysis	1. Ensifentrine 3 mg via nebulizer twice daily 2. Placebo via nebulizer twice daily	Demographics: -Mean age: 65 y -Male: 58% -Race: White: 90% Black: 3% Asian: 3% NR: 3% -Ethnicity: Hispanic or Latino: 3% -Mean post bronchodilator predicted FEV_1: 52% -Current smoker: 57% -COPD exacerbation ≤ 15 mos prior to study: 25% -Medications: LAMA: 30% LAMA/ICS: 1% LABA: 18% LABA/ICS: 20% No long-acting therapy: 30% Key Inclusion Criteria: 1.COPD patients aged 40-80 y 2. Moderate to severe COPD (mMRC ≥ 2) 3.COPD severity: Post-bronchodilator FEV_1: 30% to 70% and predicted FEV1/FVC < 0.7 4.Stable on maintenance LAMA, LABA, or ICS therapy for at least 3 months prior to enrollment Key Exclusion Criteria: 1.Asthma diagnosis 2.Hospitalized for COPD, pneumonia, or COVID-19 ≤ 12 weeks prior to enrollment 3. COPD exacerbation requiring steroids ≤ 3 months prior to enrollment	mITT over 24 wks: 1. 477 2. 283 PP over 24 wks: 1. 400 2. 245 Attrition over 24 wks: 1. 77 (16%) 2. 38 (13%) ITT over 48 wks: 1. 280 2. 89 PP over 48 wks: 1. 228 2. 70 Attrition over 48 wks: 1. 52 (19%) 2. 19 (21%)	Primary Endpoint: LSM change from baseline to week 12 in FEV_1 AUC_{0-12h} 1. 61 mL 2. -26 mL Difference: 87 mL 95% CI 55 to 119; P<0.0001 Secondary Endpoints: LSM change from baseline to week 12 in peak FEV_1 1. 204 mL 2. 57 mL Difference: 147 mL 95% CI 111 to 183; P<0.001 LSM change from baseline to week 12 in morning trough FEV_1 1. 8 mL 2. -27 mL Difference: 35 mL 95% CI 14 to 68; P=0.041 Change from baseline to week 24 in total E-RS score 1. -2.2 2. -1.3 Difference: -1.0 95% CI -1.7 to -0.2; P=0.011 Change from baseline to week 24 in total SGRQ score 1. -6.2 2. -3.9 Difference: -2.3 95% CI -4.3 to -0.3; P=0.025	NA NA NA NA NA NA	TEAE over 24 wks 1. 183 (38%) 2. 103 (36%) Serious TEAE over 24 wks: 1. 32 (7%) 2.19 (7%) TEAE leading to study withdrawal over 24 wks: 1. 19 (4%) 2. 10 (4%) TEAE from wk 24 to wk 48: 1. 58 (25%) 2. 19 (27%) P value and 95% CI NR	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not described. Randomized 5:3 to ensifentrine vs. placebo (1:1 over 24 weeks and 3:1 over 48 weeks). Stratified by COPD duration, smoking status, and background medication use. Baseline demographics balanced between groups. Performance Bias: Unclear. Double blind study design. Method of blinding not described. Not clear how placebo was different in appearance from ensifentrine. Detection Bias: Low. Outcome assessors were blinded to treatment assignment. Method of blinding not described. Attrition Bias: High. Greater than 10% over 24 weeks in both arms. Missing data were imputed using a multiple imputation approach with a missing at random assumption for continuous endpoints. Reporting Bias: Low. Study protocol available online. All outcomes reported as described. Other Bias: High. Manufacturer funded study. Four of the 7 primary authors reported funding or employment by the manufacturer. **Applicability**: Patient: Enrolled patients were primarily White. Patients using LAMA/LABA or LAMA/LABA/ICS therapy and those with COPD exacerbation < 3 months prior to enrollment were excluded, which limits generalizability to these populations. Intervention: Dosing of ensifentrine determined in phase 2 RCTs. Dose dependent increases in FEV_1 from baseline were observed. Comparator: Placebo was an appropriate comparator to determine efficacy. Comparison with current standard of care inhaler treatments is unknown. Outcomes: FDA recommended using trough FEV_1 as primary outcome. Investigators selected change in FEV_1 AUC_{0-12} at 12 weeks as primary outcome. This is an adequate outcome, but not as robust as using morning trough spirometry assessment and may indicate that the drug will wear off before the next

		4. Patients taking LABA/LAMA or LABA/LAMA/ICS therapy						dose. Changes in trough FEV_1 results were small (35 mL) which is not clinically significant., Setting: 120 Sites in 12 countries including Bulgaria, Czechia, Germany, Greece, Hungary South Korea, Poland, Romania, Russian Federation, Slovakia, United Kingdom, United States
2. Anzueto A., et al.[3] ENHANCE-2 DB, MC, PC, PG phase 3 RCT Study Duration: 24 wks	1. Ensifentrine 3 mg via nebulizer twice daily 2. Placebo via nebulizer twice daily	Demographics: -Mean age: 65 y -Male: 48% -Race: White: 95% Black: 4% Asian: < 1% NR: <1% - Ethnicity: Hispanic or Latino: 5% - Mean post bronchodilator predicted FEV_1: 51% - Current smoker: 55% - COPD exacerbation ≤ 15 mos prior to study: 21% - Medications: LAMA: 33% LAMA/ICS: 1% LABA: 7% LABA/ICS: 15% Key Inclusion Criteria: see Enhance-1 Key Exclusion Criteria: see Enhance-1	mITT: 1. 498 2. 291 PP: 1. 393 2. 218 Attrition: 1. 105 (21%) 2. 73 (25%)	Primary Endpoint: LSM change from baseline to week 12 in FEV_1 $AUC_{0\text{-}12h}$ 1. 48 mL 2. -46 mL Difference: 94 mL 95% CI 65 to 124; P<0.0001 Secondary Endpoints: LSM change from baseline to week 12 in peak FEV_1 1. 195 mL 2. 48 mL Difference: 146 mL 95% CI 113 to 179; P<0.001 LSM change from baseline to week 12 in morning trough FEV_1 1. 6 mL 2. -44 mL Difference: 49 mL 95% CI 19 to 80; P=0.002 Change from baseline to week 24 in total E-RS score 1.-2.1 2.-1.5 Difference: -0.6 95% CI -1.4 to 0.2; P=0.134 Change from baseline to week 24 in total SGRQ score 1.-4.5 2.-4.1 Difference: -0.5 95% CI -2.7 to 1.7; P=0.669	NA NA NA NA NS NS	TEAE 1. 176 (35%) 2. 103 (35%) Serious TEAE: 1. 28 (6%) 2. 17 (6%) TEAE leading to study withdrawal: 1. 35(7%) 2. 20 (7%) P value and 95% CI NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not described. Randomized 5:3 to ensifentrine vs. placebo. Stratified by COPD duration, smoking status, and background medication use. Baseline demographics balanced between groups. Performance Bias: Unclear. See Enhance-1 Detection Bias: Low. See Enhance-1 Attrition Bias: High. Both arms had high attrition (≥ 20%), primarily due to withdrawal of consent by the participant. Missing data were imputed using a multiple imputation approach with a missing at random assumption for continuous endpoints. Reporting Bias: Low. See Enhance-1 Other Bias: High. See Enhance-1 **Applicability**: Patient: See Enhance-1 Intervention: See Enhance-1 Comparator: See Enhance-1 Outcomes: See Enhance-1 Setting: 130 locations in Belgium, Bulgaria, Canada, Denmark, Estonia, Hungary, Poland, Slovakia, Spain, United States of America

Abbreviations: $AUC_{0\text{-}12h}$ = area under the curve from 0 to 12 hours; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; COVID-19 = coronavirus disease; DB = double blind; E-RS = Evaluating-Respiratory Symptoms scale; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; LSM = least square mean; mITT = modified intention to treat; mL = milliliters;; m = months; MC = multi-center; mITT = modified intention to treat; N = number of subjects; NA = not

applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PC = placebo-controlled; PG = parallel group; PP = per protocol; RCT = randomized clinical trial; SGRQ = St. George's Respiratory Questionnaire; TEAE = treatment emergent adverse effect; wks = weeks; y = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
montelukast sodium	MONTELUKAST SODIUM	ORAL	TAB CHEW	Y
montelukast sodium	SINGULAIR	ORAL	TAB CHEW	Y
montelukast sodium	MONTELUKAST SODIUM	ORAL	TABLET	Y
montelukast sodium	SINGULAIR	ORAL	TABLET	Y
montelukast sodium	MONTELUKAST SODIUM	ORAL	GRAN PACK	N
montelukast sodium	SINGULAIR	ORAL	GRAN PACK	N
zafirlukast	ACCOLATE	ORAL	TABLET	N
roflumilast	DALIRESP	ORAL	TABLET	N
roflumilast	ROFLUMILAST	ORAL	TABLET	N
zafirlukast	ZAFIRLUKAST	ORAL	TABLET	N
zileuton	ZYFLO	ORAL	TABLET	N
zileuton	ZILEUTON ER	ORAL	TBMP 12HR	N
ensifentrine	OHTUVAYRE	IH	AMPUL-NEB	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to September 04, 2024>

1	exp Asthma/dt [Drug Therapy]	41936
2	exp Pulmonary Disease, Chronic Obstructive/dt [Drug Therapy]	11385
3	exp Leukotriene Antagonists/	3275
4	Phosphodiesterase 4 Inhibitors/	1515
5	montelukast.mp.	3046
6	roflumilast.mp.	900
7	zafirlukast.mp.	644
8	zileuton.mp.	779
9	Phosphodiesterase 3 Inhibitors/ or Phosphodiesterase 4 Inhibitors/ or ensifentrine.mp.	1928
10	1 or 2	51524
11	3 or 4 or 5 or 6 or 7 or 8 or 9	8304
12	10 and 11	2381
13	limit 12 to (humans and yr="2019 -Current" and (clinical trial, phase iii or comparative study or guideline or meta-analysis or practice guideline or randomized controlled trial, veterinary or "systematic review"))	28

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OHTUVAYRE™ safely and effectively. See full prescribing information for OHTUVAYRE.

OHTUVAYRE (ensifentrine) inhalation suspension, for oral inhalation use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
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. (1)

----------DOSAGE AND ADMINISTRATION----------
Recommended Dosage: 3 mg (one ampule) twice daily administered by oral inhalation using a standard jet nebulizer with a mouthpiece. (2)
- See full prescribing information for administration instructions. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Inhalation suspension: 3 mg/2.5 mL aqueous suspension in unit-dose ampules. (3)

----------CONTRAINDICATIONS----------
OHTUVAYRE is contraindicated in patients with hypersensitivity to ensifentrine or any component of this product. (4)

----------WARNINGS AND PRECAUTIONS----------
- Should not use OHTUVAYRE to treat acute symptoms of bronchospasm. (5.1)
- If paradoxical bronchospasm occurs, discontinue OHTUVAYRE and institute alternative therapy. (5.2)
- An increase in psychiatric adverse reactions, including suicidality, were reported with use of OHTUVAYRE. Carefully weigh the risks and benefits of treatment with OHTUVAYRE in patients with a history of depression and/or suicidal thoughts or behavior. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater and equal to 1% and more common than placebo) include back pain, hypertension, urinary tract infection, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Verona Pharma at 888-672-0371 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Hepatic impairment: Ensifentrine exposure increases in patients with hepatic impairment. Use with caution. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

Appendix 4: Key Inclusion Criteria

Population	Adults aged 40 to 80 years with moderate to severe COPD
Intervention	See Appendix 1
Comparator	See Appendix 1
Outcomes	Change in forced expiratory volume in one second (FEV_1) area under the curve from 0 to 12 hours ($AUC_{0\text{-}12h}$), reduction in COPD exacerbations and hospitalizations, improved quality of life
Timing	12 weeks
Setting	Outpatient

Roflumilast, Oral

Goals:

- Decrease the number of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and with a history of exacerbations.

Length of Authorization:

- Up to 12 months

Requires PA:

- Oral roflumilast (Daliresp®) tablets.
- This PA does not apply to requests for topical roflumilast (Zoryve®) which are subject to separate clinical PA criteria.

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have documented severe or very severe COPD (e.g., FEV_1 of $\leq$ 50% predicted)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny for medical appropriateness
4. Does the patient have a diagnosis of chronic bronchitis (ICD10 J410-J42; J440-J449)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny for medical appropriateness
5. Does the patient have documented prior COPD exacerbations?	**Yes:** Go to #6	**No:** Pass to RPh. Deny for medical appropriateness

Approval Criteria		
6. Does the patient have an active prescription for a long-acting bronchodilator (long-acting anticholinergic agent or long-acting beta-agonist) and inhaled corticosteroid (ICS)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; recommend trial of preferred long-acting bronchodilator and ICS
7. Is the prescriber a specialist in respiratory medicine or is the request in consultation with a specialist?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Does the provider attest that the patient's condition improved with roflumilast treatment?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny for medical appropriateness

P&T/DUR Review: *12/24 (DM); 10/20 (KS), 9/15; 5/13; 2/12*
Implementation: *1/1/25; 11/1/20; 10/15; 1/14; 5/12*

Targeted Immune Modulators for Severe Asthma and Atopic Dermatitis

Goal(s):

- Promote use that is consistent with national clinical practice guidelines, medical evidence, and OHP-funded conditions. Allow case-by-case review for members covered under the EPSDT program.
- Promote use of cost-effective products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All targeted immune modulators with indications for severe asthma, atopic dermatitis, or other indications (see **Table 1** below) for both pharmacy and physician-administered claims.
- This PA does not apply to topical agents for inflammatory skin conditions which are subject to separate clinical PA criteria.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Indications and Ages

Generic Name/ BRAND NAME	Eosinophilic Asthma	Moderate to Severe Allergic Asthma	Difficult To Treat, Severe Asthma	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Eosinophilic Esophagitis	Atopic Dermatitis (AD)	Food Allergy Avoidance	Other
Abrocitinib CIBINQO						≥12 yrs		
Benralizumab FASENRA	≥6 yrs							EPGA ≥18 yrs
Dupilumab DUPIXENT	≥6 yrs (or with oral corticosteroid dependent asthma)			≥12 yrs	≥1 yr & weighing ≥15 kg	≥6 months	≥18 yrs	PN ≥18 yrs COPD ≥18 yrs
Mepolizumab NUCALA	≥6 yrs			≥18 yrs				HES ≥ 12 yrs EPGA ≥18 yrs
Omalizumab XOLAIR		≥6 yrs		≥18 yrs			≥ 1 yo	CSU ≥ 12 yrs
Reslizumab CINQAIR	≥18 yrs							

Tezepelumab TEZSPIRE			≥ 12 yrs					
Tralokinumab ADBRY						≥12 yrs		

Table 2. Recommended First-Line Conventional Treatments

Indication	Conventional treatment
Atopic Dermatitis	4-week trial of either one the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) in combination with a topical calcineurin inhibitor (e.g., tacrolimus) OR • Oral immunomodulator therapy (e.g., cyclosporine, methotrexate, or oral corticosteroids)?
Eosinophilic granulomatosis with polyangiitis (EGPA)	4-week trial of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)
Nasal polyps	Intranasal corticosteroids (2 or more courses administered for at least 12 weeks each)
Asthma	Maximally dosed inhaled corticosteroid (**Table 3**) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)
Eosinophilic esophagitis	• Proton pump therapy for at least 8 weeks OR • Corticosteroid therapy with local administration of fluticasone multi-use inhaler for at least 8 weeks (use nasal inhaler and swallow contents of the spray).
Chronic Obstructive Pulmonary Disease (COPD)	• Triple inhaler therapy (inhaled corticosteroid (ICS) with long-acting beta agonist (LABA) and long-acting muscarinic antagonist (LAMA) inhalers) for at least 3 months
Other	Documentation for conventional treatment(s) are not required

Table 3. Maximum Adult Doses for Inhaled Corticosteroids

High Dose Corticosteroids:	Maximum Dose
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID

Alvesco (ciclesonide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Armonair (fluticasone propionate)	232 mcg BID
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
AirDuo Digihaler (fluticasone/salmeterol)	232/14 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	232/14 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 4. Required baseline documentation of disease severity

Indication	Disease severity definitions
Atopic dermatitis or prurigo nodularis	Functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on another validated tool) AND one or more of the following: • At least 10% body surface area involved, or • Hand, foot, face, or mucous membrane involvement
Asthma	• At least 4 asthma exacerbations requiring systemic corticosteroids in the previous 12 months OR • taking continuous oral corticosteroids at least the equivalent of prednisolone 5 mg per day for the previous 6 months OR • at least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while on conventional treatment outlined in **Table 2 and 3**
IgE-mediated food allergy	• Number of epinephrine administrations and hospital/emergency department visits (if any) in past 12 months which were caused by presumed exposure to food that triggered an allergic response
Hypereosinophilic syndrome (HES)	• Duration of disease of at least 6 months without an identifiable non-hematologic secondary cause

Chronic Obstructive Pulmonary Disease (COPD)	• Blood eosinophil count ≥ 300 cells/µL AND • at least 1 hospitalization or ≥ 2 emergency department (ED) visits in the past 12 months while on conventional treatment outlined in **Table 2 and 3**

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved age and indication (**Table 1**)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria and mild-to-moderate atopic dermatitis are not OHP-funded conditions	**Yes**: Go to #5	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP. If eligible for EPSDT review: Go to #4
4. Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical necessity.
5. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
7. Is the medication being prescribed by, or in consultation with, an appropriate specialist? Examples include allergist for any condition, dermatologist for atopic dermatitis, otolaryngologist for nasal polyps, or pulmonologist for asthma	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is there documentation of failure to have benefit with, or contraindication to, recommended conventional first-line treatments options (**Table 2 and 3**)?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is there documentation of disease severity prior to initiation of a targeted immune modulator (**Table 4**)?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the request for treatment of difficult to treat, severe asthma? Note: Difficult to treat, severe asthma is defined as asthma with poor symptom control on high-dose inhaled corticosteroid-long-acting beta agonist (ICS-LABA) or maintenance oral corticosteroids (OCS).	**Yes:** Go to #11	**No:** Go to #13
11. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the patient currently receiving another monoclonal antibody (e.g., dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, tezepelumab etc.) without documentation indicating the patient is switching between treatments?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. Is the request for eosinophilic asthma, allergic asthma, or food allergies?	**Yes:** Go to #14	**No:** Go to #15

Approval Criteria		
14. Is there diagnostic documentation for the requested indication? • Eosinophilic asthma: blood eosinophil count ≥150 cells/µL OR fractional exhaled nitric oxide (FeNO) ≥25 ppb in the past 12 months • Allergic IgE-mediated asthma: positive skin test OR in vitro reactivity to perennial allergen • Food allergy: IgE-mediated food allergy with skin testing to confirm allergy OR in vitro reactivity to perennial allergen	**Yes:** Approve for up to 12 months. Document test and result:_____	**No:** Pass to RPh. Deny; medical appropriateness.
15. Is the request for a JAK inhibitor (e.g., abrocitinib)?	**Yes:** Go to #16	**No:** Go to #17
16. Has the patient failed to have benefit with or have intolerance or contraindication to alternative targeted immunodulatory therapy?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.
17. Duration of approval based on indication:	Asthma, COPD, hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis, and chronic spontaneous urticaria: 12 months All other conditions: requested duration or 6 months, whichever is less	

Renewal Criteria		
1. Is the request to renew therapy for inflammatory skin disease?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Have the patient's symptoms improved with targeted immune modulator therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (CDLQI from when treatment started OR • at least a 2-point improvement on the Investigators Global Assessment (IGA) score?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for asthma or COPD?	**Yes:** Go to #4	**No:** Go to #6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium) for asthma or triple inhaler therapy (ICS/LABA/LAMA) for COPD?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the number of emergency department (ED) visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline or has the number of COPD exacerbations decreased?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request to renew therapy for another FDA approved indication?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have the patient's symptoms improved with therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed May 2, 2023.*
2. National Institute for Health and Care Excellence (NICE) Guidance. Mepolizumab for Treating Severe Eosinophilic Asthma. https://www.nice.org.uk/guidance/ta671 February 2021.

3. National Institute for Health and Care Excellence (NICE) Guidance. Dupilumab for Treating Severe Asthma with Type 2 Inflammation. https://www.nice.org.uk/guidance/ta751 December 2021
4. Global Initiative for Asthma. Global strategy for asthma management and prevention (2021 update). 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf

P&T Review: *12/24 (DM), 8/24; 6/23; 10/22; 6/22; 8/2; 10/20,7/19; 7/18; 7/16*
Implementation: *1/1/25; 9/1/24; 7/1/23; 1/1/23; 7/1/22; 1/1/22*

Ensifentrine

Goals:

- Promote use that is consistent with national clinical practice guidelines and medical evidence in people with COPD.

Length of Authorization:

- Up to 12 months

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have COPD?	**Yes:** Go to #4	No: Pass to RPh. Deny for medical appropriateness
4. Does the patient have an active prescription for a long-acting bronchodilator (long-acting anticholinergic agent or long-acting beta-agonist) or an inhaled corticosteroid (ICS)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; recommend trial of preferred long-acting bronchodilator and ICS
5. Is the prescriber a specialist in respiratory medicine or is the request in consultation with a specialist?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Does the provider attest that the patient's condition improved with ensifentrine treatment?	**Yes:** Approve for 12 months.	**No:** Pass to RPh. Deny for medical appropriateness

P&T/DUR Review: *12/24 (DM)*
Implementation: *TBD*

Author: Moretz December 2024