COPD is associated with substantial respiratory-related and total healthcare costs. In 2010, the total annual cost of COPD in the United States was an estimated $49.9 billion, of which $29.5 billion accounted for direct costs, $8 billion for indirect costs for associated morbidity, and $12.4 billion for indirect costs related to COPD mortality.4

COPD is frequently misdiagnosed and may go undetected for years.11 The early diagnosis and appropriate management of COPD are essential, because COPD may worsen over time. Effective management can help control symptoms, reduce the risk of exacerbations and complications, slow disease progression, and, in some cases, can improve a person’s ability to lead an active life.11

Therapeutic goals for COPD include preventing and treating exacerbations, reducing hospitalizations and mortality, relieving dyspnea that restricts activity, and increasing exercise tolerance and health-related quality of life.12 Smoking cessation is crucial for smokers with COPD.11 Pharmacologic treatments include bronchodilators (short-acting and long-acting), inhaled steroids, oral steroids, combination inhalers, phosphodiesterase-4 inhibitors, theophylline, and antibiotics. Other therapies include oxygen therapy and lifestyle changes. Surgery may also be an option for some patients with severe disease who do not respond to other treatments.11

Breo Ellipta: A New, Fixed-Dose Combination Inhaler Approved for COPD

On May 10, 2013, the US Food and Drug Administration (FDA) approved Breo Ellipta (fluticasone furoate/vilanterol inhalation powder) as oral inhalation for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. Fluticasone furoate/vilanterol is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. Fluticasone furoate/vilanterol is not indicated for the relief of acute bronchospasm or for the treatment of asthma, and is not recommended in patients younger than age 18 years.13,14

Curtis J. Rosebraugh, MD, MPH, Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research at the FDA, stated, “The availability of new long-
term maintenance medications provides additional treatment options for the millions of Americans who suffer with COPD.13

The safety and efficacy of fluticasone furoate/vilanterol were evaluated in studies that included 7700 patients with a clinical diagnosis of COPD.11 As part of the approval, the FDA required that fluticasone furoate/vilanterol be accompanied by a patient medication guide with instructions for use and information about the potential risks of taking the drug.13

The prescribing information for fluticasone furoate/vilanterol includes a Boxed Warning stating that long-acting beta-adrenergic agonists (LABAs), such as vilanterol, one of the ingredients in this combination, are associated with an increased risk of asthma-related death. It also states that the safety and efficacy of fluticasone furoate/vilanterol in patients with asthma have not been established, and that it is not indicated for the treatment of asthma.14

Mechanism of Action

Fluticasone furoate/vilanterol contains 2 different classes of drugs—fluticasone furoate, a synthetic trifluorinated corticosteroid, and vilanterol, a LABA. Each of these 2 drugs has a different mechanism of action.

**Fluticasone Furoate**

Fluticasone furoate, a synthetic trifluorinated corticosteroid, has anti-inflammatory activity and has been shown in vitro to have a binding affinity for the glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these in vitro results is unknown.19

The precise mechanism through which fluticasone furoate affects the symptoms of COPD is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types and mediators. In vitro and in vivo models have demonstrated specific effects of fluticasone furoate, including activation of the glucocorticoid response element, inhibition of proinflammatory transcription factors (eg, nuclear factor-kappa beta), and inhibition of antigen-induced lung eosinophilia in sensitized rats.14

**Vilanterol Inhalation Powder**

Vilanterol inhalation powder was shown to have a functional selectivity similar to salmeterol based on in vitro tests. The clinical relevance of this in vitro finding is unknown. The pharmacologic effects of beta-2 adrenoceptor agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate to 3’,5’-cyclic-adenosine monophosphate (cAMP). Increased cAMP levels cause relaxation of bronchial smooth muscle and inhibition of the release of mediators of immediate hypersensitivity from cells, especially from mast cells.14

**Dosing**

Fluticasone furoate/vilanterol is indicated for oral inhalation only. The recommended dosage for maintenance treatment of COPD is 1 inhalation of fluticasone furoate 100 mcg/vilanterol 25 mcg once daily.

The fluticasone furoate/vilanterol inhaler contains 2 double-foil blister strips of powder formulation for oral inhalation: one strip contains fluticasone furoate 100 mcg per blister, and the other contains vilanterol 25 mcg per blister.14

**Clinical Studies**

The FDA approval of fluticasone furoate/vilanterol was based on 4 confirmatory trials (of 6- and 12-months’ duration), 3 active comparator trials (of 12 weeks’ duration), and dose-ranging trials of shorter duration.14

Findings from 2 of the confirmatory trials related to lung function are highlighted below. Of the 2254 patients enrolled in these 2 trials, 70% were male and 84% were Caucasian (mean age, 62 years), with an average smoking history of 44 pack-years; 54% of the patients were identified as current smokers. In these 2 trials, all treatments were administered as 1 inhalation once daily.14

**Confirmatory Lung Function Trial 1**

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study that evaluated the efficacy of 2 strengths of fluticasone furoate/vilanterol on lung function in patients with COPD (Table 1).

In this study, fluticasone furoate/vilanterol demonstrated rapid and significant sustained improvement in forced expiratory volume in 1 second (FEV1) in patients with moderate-to-severe COPD, which was not influenced by the dose.14,15

**Confirmatory Lung Function Trial 2**

In trial 2, a 24-week, randomized, double-blind, placebo-controlled study, combination therapy with fluticasone furoate 100 mcg/vilanterol 25 mcg significantly improved the weighted mean FEV1 (173 mL) and trough FEV1 (115 mL) versus placebo (P <.001) in patients with moderate-to-severe COPD (Table 2).14,16 All treatments in this study were well-tolerated.16

Overall, fluticasone furoate 100 mcg/vilanterol 25 mcg resulted in a larger increase in the weighted mean FEV1 (from 0 hours to 4 hours) compared with placebo.
and with fluticasone furoate 100 mcg at day 168. At day 169, trials 1 and 2 showed a significant increase in trough \( \text{FEV}_1 \) for all strengths of fluticasone furoate/vilanterol compared with placebo.\(^{14}\)

### Adverse Events and Contraindications

The most common adverse reactions (incidence, \( \geq 3\% \)) associated with fluticasone furoate/vilanterol are nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis.\(^{14}\)

Fluticasone furoate/vilanterol is contraindicated in patients with severe hypersensitivity to milk proteins or those who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

### Warnings and Precautions

Fluticasone furoate/vilanterol should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD, or as rescue therapy for the treatment of acute episodes of bronchospasm, which should be treated with an inhaled, short-acting beta-2 agonist.\(^{14}\)

Fluticasone furoate/vilanterol should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABAs, because an overdose may result.

Oropharyngeal candidiasis has occurred in patients treated with fluticasone furoate/vilanterol. Patients should be monitored periodically and be advised to rinse
the mouth without swallowing after inhalation of this agent to help reduce this risk of infection.

There is an increased risk for pneumonia in patients with COPD who are taking fluticasone furoate/vilanterol. Patients should be monitored for signs and symptoms of pneumonia.

Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients.

There is an increased risk of impaired adrenal function when patients are transferred from systemic corticosteroids. Patients should be tapered slowly from systemic corticosteroids when being transferred to fluticasone furoate/vilanterol.

Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage of inhaled corticosteroids in susceptible individuals. If such changes occur, fluticasone furoate/vilanterol should be discontinued slowly.

Inhaled medications can produce paradoxical bronchospasm, which may be life-threatening. Vilanterol, the LABA in the fluticasone furoate/vilanterol combination, can produce clinically significant cardiovascular effects in some patients. Decreases in bone mineral density have been observed with long-term administration of products containing inhaled corticosteroids, as have glaucoma, increased intraocular pressure, and cataracts. It is recommended that patients be monitored for decreased bone mineral density, glaucoma, and cataracts.

Fluticasone furoate/vilanterol should be used with caution in patients with cardiovascular disorders, especially those with coronary insufficiency, cardiac arrhythmias, and hypertension, because of beta-adrenergic stimulation.

Caution should be exercised when considering the coadministration of fluticasone furoate/vilanterol with long-term ketoconazole and other known strong CYP3A4 inhibitors, because increased systemic corticosteroid and cardiovascular adverse effects may occur.

Fluticasone furoate/vilanterol should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. Clinicians should also be alert to hypokalemia and hyperglycemia.

Conclusion

A new treatment option for COPD became available in May 2013 when Breo Ellipta (fluticasone furoate/vilanterol) received FDA approval for the long-term, once-daily maintenance treatment of airflow obstruction and for reducing exacerbations in patients with COPD. Breo Ellipta is a fixed-dose combination of fluticasone furoate 100 mcg, an inhaled corticosteroid, and vilanterol 25 mcg, a LABA.

Fluticasone furoate/vilanterol was shown to improve lung function and reduce exacerbations compared with placebo in several clinical trials that included a total of 7700 patients with a clinical diagnosis of COPD. The most common adverse reactions reported with fluticasone furoate/vilanterol in clinical trials were nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis.

References