Chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema, is a serious and progressive disease characterized by difficulty breathing, productive cough, shortness of breath, and chest tightness. The leading causes of COPD are smoking and exposure to secondhand smoke. Other risk factors for COPD include extended exposure to air pollution, various chemicals, and dust, as well as heredity, a history of childhood respiratory infections, and socioeconomic status. In the United States, an estimated 12.7 million adults have COPD.

COPD is the third most common cause of death in the United States. The symptoms of COPD significantly limit daily activities and negatively affect the patient’s quality of life. Approximately 50% of all patients with COPD are hindered in their ability to work, because of their symptoms. In patients with COPD, the pulmonary airflow is poor for multiple reasons, including the airways and air sacs lose their elasticity, the walls between air sacs are destroyed, the airway walls are thick and inflamed, and mucus production is high. The diagnosis of COPD is made by spirometry, as well as by the assessment of clinical symptoms and risk factors. Therapy for COPD is designed to stabilize the disease and to prevent acute exacerbations. Initial pharmacologic treatment is comprised of bronchodilators in the form of either a short-acting beta2-agonist (SABA) or a short-acting muscarinic antagonist. As the disease progresses and the patient experiences more frequent acute exacerbations of COPD, inhaled corticosteroids are used in combination with a long-acting beta2-agonist (LABA) or a long-acting muscarinic antagonist (LAMA). Some patients may be candidates for surgical intervention if they have refractory, advanced-stage COPD.

Nonpharmacologic interventions also play a significant role in reducing symptoms and in improving the quality of life for patients with COPD. Patients should also undergo pulmonary rehabilitation, which includes 6 weeks of exercise, nutrition counseling, psychosocial support, disease education, and smoking cessation for those who smoke. Although smoking cessation is the single most effective intervention to improve outcomes in COPD, less than 33% of patients maintain abstinence. Those who do stop smoking often continue to have shortness of breath and other symptoms of limited airflow.

In addition to therapies approved by the US Food and Drug Administration (FDA), more than 50 new medications are currently in development for the treatment of COPD, including ultra-LABAs, LAMAs, and combination bronchodilator and inhaled corticosteroid therapies, as well as novel agents that target CD8+ T-cells, nuclear factor-κB, chemokine receptors 2 and 3, T-helper 17 cells, and MAP kinase p38. However, the COPD management approach remains primarily palliative; there is currently no cure for COPD, and none of the currently available therapies can prevent lung function decline or airway destruction.

In 2010, the cost associated with COPD in the United States was calculated at the staggering amount of approximately $50 billion. The mean cost was projected to be more than $4000 per patient annually, and is expected to rise as more patients are diagnosed with COPD. Direct healthcare costs account for the majority of COPD-related expenses and include physician office visits, hospitalizations, home care, and medications.

The cost burden of COPD rises with increasing disease severity. Patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I COPD spend the lowest amount ($1681 per patient annually), GOLD stage II COPD costs approximately $5000 per patient annually, and GOLD stage III COPD costs more than $10,800 per patient annually. Many patients with COPD also have comorbidities, such as cardiovascular disease, lung cancer, and diabetes, which incur additional expenses.

A Novel Combination Therapy for COPD

In December 2013, the FDA approved umeclidinium/vilanterol inhalation powder (Anoro Ellipta; GlaxoSmithKline) for the once-daily long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. Umeclidinium and vilanterol inhalation powder (henceforth, umeclidinium/vilanterol) is the first COPD treatment that contains 2 long-acting bronchodilators—a LAMA and a LABA—in 1 inhaler.
The safety and efficacy of umeclidinium/vilanterol have been evaluated in more than 2400 patients diagnosed with COPD. The FDA approval of this new combination therapy was based on the demonstration of safety and improved lung function in a double-blind, placebo-controlled, parallel-group, phase 3 study of more than 1500 patients with COPD, including current and former smokers.8

“Anoro Ellipta works by helping the muscles around the airways of the lungs stay relaxed to increase airflow in patients with COPD,” said Curtis J. Rosebraugh, MD, MPH, Director of the Office of Drug Evaluation II in the FDA’s Center for Drug Evaluation and Research. “The availability of new long-term maintenance medications provides additional treatment options for the millions of Americans who suffer with COPD.”

The FDA approved this new combination with a patient medication guide that provides instructions for patients on how to use it as well as the potential risks involved in using this inhaled therapy.

**Mechanism of Action**

The active agents—umeclidinium and vilanterol—that are combined in this new inhalation powder involve 2 different mechanisms of action according to the individual components of this medication and have therefore different and combined effects in the lungs.

Umeclidinium is a LAMA (anticholinergic) that affects muscarinic receptors M1 through M5. In the airways, it causes bronchodilation by inhibiting the M3 receptor at the smooth muscle.

Vilanterol, a LABA, stimulates intracellular adenyl cyclase, which leads to an increase in cyclic-3’,5’-adenosine monophosphate levels, relaxation of bronchial smooth muscle, and inhibition of inflammatory mediators.

**Dosing and Administration**

For COPD maintenance, the new inhalation powder, which contains umeclidinium 62.5 mcg and vilanterol 25 mcg, is administered as 1 inhalation once daily through the mouth.9

Umeclidinium/vilanterol should be used orally at the same time every day and should not exceed 1 oral inhalation every 24 hours. No dose adjustment is needed for older patients, patients with renal impairment, or patients with moderate hepatic impairment.9

**The active agents—umeclidinium and vilanterol—that are combined in this new inhalation powder involve 2 different mechanisms of action according to the individual components of this medication and have therefore different and combined effects in the lungs.**

**Pivotal Phase 3 Clinical Trial**

The phase 3 clinical trial that led to the FDA approval was a multicenter, parallel-group study with 1532 patients who were randomly assigned to 24 weeks of 1 of 4 groups: umeclidinium/vilanterol, umeclidinium alone, vilanterol alone, or to placebo. The patients (aged ≥40 years) enrolled in this trial were current or former cigarette smokers with a clinically established history of COPD. The primary efficacy end point was predose trough forced expiratory volume in 1 second (FEV1) on treatment day 169.

Secondary end points included the number of patients who responded to umeclidinium/vilanterol, to umeclidinium, or to vilanterol according to FEV1 at day 1, and patients who had a larger change from baseline in 0- to 6-hour weighted mean FEV1 on day 14 with umeclidinium/vilanterol compared with umeclidinium or vilanterol alone. Other outcomes measured were the mean Transition Dyspnea Index focal score, the mean Shortness of Breath with Daily Activities score, rescue

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**Table 1  Efficacy Results of Phase 3 Trial of Umeclidinium 62.5 mcg/Vilanterol 25 mcg Combination**

<table>
<thead>
<tr>
<th>Efficacy measure</th>
<th>Umeclidinium 62.5 mcg/ vilanterol 25 mcg vs placebo</th>
<th>Umeclidinium 62.5 mcg vs placebo</th>
<th>Vilanterol 25 mcg vs placebo</th>
<th>Umeclidinium/ vilanterol alone vs umeclidinium alone</th>
<th>Umeclidinium/ vilanterol alone vs vilanterol alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough FEV1 at day 169</td>
<td>0.167 L (P &lt; .001)</td>
<td>0.115 L (P &lt; .001)</td>
<td>0.072 L (P &lt; .001)</td>
<td>0.052 L (P = .004)</td>
<td>0.095 L (P &lt; .001)</td>
</tr>
<tr>
<td>Increase from baseline 0-6 hr weighted mean FEV1 at day 168</td>
<td>0.242 L (P &lt; .001)</td>
<td>0.15 L (P &lt; .001)</td>
<td>0.122 L (P &lt; .001)</td>
<td>0.092 L (P &lt; .001)</td>
<td>0.12 L (P &lt; .001)</td>
</tr>
</tbody>
</table>

FEV1 indicates forced expiratory volume in 1 second.


FEV1 indicates forced expiratory volume in 1 second.
salbutamol use, the time to first COPD exacerbation, and the St George’s Respiratory Questionnaire (SGRQ) quality-of-life score.8

**Patient Population**

Of 2210 patients with COPD who were screened for the phase 3 trial, 1532 patients were included in the intent-to-treat (ITT) analysis of this study.8 A total of 1178 patients with moderate-to-severe COPD completed the study.8

Patient demographics and baseline characteristics were similar among the treatment groups. The median age of participants ranged from 62 to 64 years.8 Approximately 70% of the patients were male, and approximately 50% of the patients were smokers at screening. The large majority of patients were in GOLD stage II or III.8

**Efficacy**

The phase 3 clinical trial demonstrated that the combination of umeclidinium and vilanterol is safe and efficacious in patients with moderate-to-severe COPD. Compared with each of these agents administered as monotherapy, the umeclidinium 62.5-mcg/vilanterol 25-mcg combination demonstrated significant improvements in predose trough FEV1, as well as in 0- to 6-hour weighted mean FEV1 (Table 1).8

In the ITT population, treatment with umeclidinium 62.5 mcg/vilanterol 25 mcg resulted in a significant 0.112-L improvement in FEV1 after 15 minutes (first assessment) compared with placebo. A 0.273-L increase from baseline in peak FEV1 was seen over 6 hours on day 1 for the umeclidinium 62.5-mcg/vilanterol 25-mcg combination.8 Improvements in lung function observed with the umeclidinium/vilanterol combination were considered clinically meaningful compared with umeclidinium or vilanterol as monotherapy.8

The results of secondary end point analyses favored the active treatment arms compared with placebo. The 3 active treatments resulted in lower use of rescue inhaler, improvement in SGRQ score, and a lower risk for COPD exacerbation compared with placebo.8

**Adverse Effects/Safety**

The most frequent treatment-emergent adverse effects in the phase 3 study of umeclidinium/vilanterol included headache, nasopharyngitis, upper respiratory tract infection, and cough.8 These reactions were seen with similar frequency in the 3 active treatment groups.8

The adverse effects that led to study withdrawal were infrequent and were related to worsening COPD. A total of 9 patients died of adverse events, including 3 in the umeclidinium 62.5-mcg/vilanterol 25-mcg group, 3 in the vilanterol 25-mcg group, and 3 in the umeclidinium 62.5-mcg group.

In addition to the pivotal phase 3 trial, the overall clinical program for umeclidinium/vilanterol included more than 8000 patients with COPD in different clinical trials.9

Table 2 lists the most common adverse reactions associated with the umeclidinium/vilanterol combination that were reported in four 6-month trials: 2 placebo-controlled trials (Trial 1, N = 1532; Trial 2, N = 1489) and 2 active-controlled trials (Trial 3, N = 843; Trial 4, N = 869).8,9

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Adverse Events with Umeclidinium/Vilanterol Inhalation Powder with ≥1% Incidence in Patients with COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>Placebo, % (N = 555)</td>
</tr>
<tr>
<td>Infections/infestations</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal/connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neck pain</td>
<td>&lt;1</td>
</tr>
<tr>
<td>General disorders/administration-site conditions</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease.

Source: Anoro Ellipta (umeclidinium and vilanterol inhalation powder) prescribing information; 2013.
Contraindications
Umeclidinium/vilanterol is contraindicated in patients with severe hypersensitivity to milk proteins or to any of the product’s ingredients.9

Warnings and Precautions
Boxed warning. Umeclidinium/vilanterol includes a boxed warning that LABAs, such as vilanterol, increase the risk for asthma-related death. No trial has been conducted to determine if the rate of asthma-related death is increased in patients taking umecclidinium/vilanterol. This medication is not indicated for the treatment of asthma.9

Disease deterioration. Because it has not been studied in patients during rapidly deteriorating or potentially life-threatening episodes of COPD, umecclidinium and vilanterol inhalation powder should not be used in such patients.9 The oral inhalation powder should not be used for the relief of acute symptoms (ie, as rescue therapy in acute episodes of bronchospasm); there are no studies of umecclidinium/vilanterol in these situations.9 Acute bronchospasm symptoms should be treated with an inhaled SABA.9 Patients who are taking an oral or inhaled SABA on a regular basis (eg, 4 times daily) should discontinue administration in this fashion. SABAs should be used only for the symptomatic relief of acute COPD symptoms.9

If signs of COPD deterioration occur while taking the combination inhalation powder, which include inadequate control of bronchoconstriction symptoms, lowered efficacy of SABA therapy, or higher-than-recommended use of SABAs, physicians should promptly review the patient’s COPD treatment regimen. The daily dose should not be increased beyond the recommended dose in this situation.9

Overuse/use with other LABAs. To prevent over-dose, the oral inhalation powder should not be used more often than studies of SABA, or higher-than-recommended use of SABAs, physicians should promptly review the patient’s COPD treatment regimen. The daily dose should not be increased beyond the recommended dose in this situation.9

Paradoxical bronchospasm. Like other inhaled medicines, umecclidinium/vilanterol can lead to life-threatening paradoxical bronchospasm. If paradoxical bronchospasm occurs, the patient should use an inhaled, short-acting bronchodilator immediately and umecclidinium/vilanterol should be discontinued.9

Hypersensitivity reactions. The administration of umecclidinium/vilanterol, which contains lactose, can result in hypersensitivity reactions. Anaphylactic reactions have occurred in patients with severe milk protein allergy after the inhalation of other powder products containing lactose.9 Patients with severe milk protein allergy should not use this medication.9

Cardiovascular effects. As a beta-agonist, vilanterol can cause clinically significant cardiovascular adverse effects in some patients. The discontinuation of this treatment should be considered in patients who exhibit such effects. Although the clinical significance is unknown, beta agonists have also been reported to produce electrocardiographic changes, including T-wave flattening, corrected QT interval prolongation, and ST-segment depression. Patients with cardiovascular disorders, particularly coronary insufficiency, arrhythmias, and hypertension, should use umecclidinium/vilanterol with caution.9

Coexisting conditions. Because umecclidinium/vilanterol contains sympathomimetic amines, it should be used with caution in patients with convulsive disorders or thyrotoxicosis, as well as in patients who are unusually responsive to sympathomimetic amines.9

Worsening of narrow-angle glaucoma. Patients with narrow-angle glaucoma should use this medication with caution. Patients should be aware of the signs and symptoms of acute narrow-angle glaucoma and should immediately consult a physician if such problems develop.9

Urinary retention. Umeclidinium/vilanterol should be used with caution in patients with urinary retention, particularly prostatic hyperplasia and bladder-neck obstruction.9

Hypokalemia and hyperglycemia. Some patients who take beta-adrenergic agonists may exhibit significant hypokalemia that can lead to adverse cardiovascular effects. Beta-agonist medications may also result in transient hyperglycemia in some patients. Umeclidinium/vilanterol did not affect serum glucose or potassium levels in 4 clinical trials that lasted 6 months.9

Use in Specific Populations
Umeclidinium/vilanterol has a pregnancy category C. The combination and its individual components have not been studied in well-controlled trials of pregnant women specifically.9

There are also no adequate trials evaluating umeclidinium/vilanterol during labor and delivery. Because beta-agonists can affect uterine contractility, the use of this combination during labor should be considered only if the potential benefit justifies the potential risk.9

Caution should also be exercised when administering umecclidinium/vilanterol to a nursing woman. It is not known whether either drug is excreted in human breast milk.9

The safety and efficacy of umecclidinium/vilanterol in pediatric patients have not been established.9

Clinical trials of umecclidinium/vilanterol for COPD included 2143 patients aged ≥65 years.9 When compar-
Umeclidinium/vilanterol inhalation powder is the first FDA-approved once-daily maintenance treatment for COPD that combines 2 long-acting bronchodilators with 2 distinct and complementary mechanisms of action.

Conclusion

Umeclidinium/vilanterol inhalation powder is the first FDA-approved once-daily maintenance treatment for COPD that combines 2 long-acting bronchodilators with 2 distinct and complementary mechanisms of action. Umeclidinium/vilanterol has been shown effective and safe in multiple clinical trials of patients with moderate-to-severe COPD. This new combination therapy offers a convenient treatment option for patients with COPD who require long-term maintenance therapy.

References