Formulary Drug Reviews

Umeclidinium Bromide and Vilanterol Trifenatate Inhalation Powder

Dennis J. Cada, PharmD, FASHP, FASCP (Editor)*; Kyle Ingram, PharmD†; James Leonard‡; and Daniel E. Baker, PharmD, FASHP, FASCP§

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Generic Name:	Umeclidinium bromide and vilanterol trifenatate inhalation powder
Proprietary Name:	Anoro Ellipta (GlaxoSmithKline)
Approval Rating:	1S
Therapeutic Class:	Respiratory inhalant combination; long-acting muscarinic antagonist (LAMA)/long-acting beta agonist (LABA)
Similar Drugs:	Formoterol, fluticasone/vilanterol, ipratropium, ipratropium/albuterol, salmeterol, tiotropium bromide
Sound- or Look-Alike Names:	Fluticasone/vilanterol

INDICATIONS

Umeclidinium bromide/vilanterol trifenatate inhalation powder is indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.¹

Umeclidinium/vilanterol is not indicated for the relief of acute bronchospasm or asthma.¹

There are no other fixed-dose, long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA) combination products currently approved in the United States. Combination short-acting beta-agonist and short-acting anticholinergic products are available; however, their use is limited by frequent dosing requirements.^{2,3} Table 1 summarizes the US Food and Drug Administration (FDA)-approved indications for inhaled combination muscarinic and beta-2 agonists.

CLINICAL PHARMACOLOGY

In COPD, acetylcholine is released to airway smooth muscle and acts reversibly through postsyn-

*Founder and Contributing Editor, *The Formulary*; †Drug Information Resident, Drug Information Center, Washington State University, Spokane, Washington; ‡Drug Information Intern, Drug Information Center, Washington State University; §Director, Drug Information Center, and Professor of Pharmacy Practice, College of Pharmacy, Washington State University Spokane, PO Box 1495, Spokane, Washington 99210-1495. The authors indicate no relationships that could be perceived as a conflict of interest.

Table 1. FDA-approved indications for inhaled combination muscarinic antagonists and beta-2 agonists¹⁻³

Indications	Umeclidinium bromide/ vilanterol trifenatate inhalation powder (<i>Anoro Ellipta</i>)	Ipratropium bromide/ albuterol sulfate inhalation spray (<i>Combivent Respimat</i>)	Ipratropium bromide/albuterol sulfate inhalation solution (<i>DuoNeb</i>)
COPD; maintenance therapy	X		
Bronchospasm associated with COPD in patients requiring > 1 bronchodilator		X	X

Note: COPD = chronic obstructive pulmonary disease.

aptic muscarinic receptors to mediate airway smooth contraction and mucus secretion. Inhaled anticholinergic agents block muscarinic receptors on airway smooth muscle to inhibit bronchoconstriction.⁴ The M3 receptor is highly expressed in human airway smooth muscle. Activation of the M3 receptor in smooth muscle tissue of the lungs leads to an increase in intracellular calcium levels, which results in bronchoconstriction, whereas inhibition ultimately results in bronchodilation.^{1,5}

Umeclidinium is a LAMA, also referred to as an antimuscarinic. Umeclidinium has affinity for M1 through M5 receptors, with greater affinity for M3 than M2 receptors and similar receptor affinities to tiotropium.^{1,5} In vitro studies suggest that dissociation of umeclidinium from the M2 receptor is 8 times faster than from the M3 receptor and 4 times faster than tiotropium, suggesting that blockade of presynaptic M2 receptors is limited. In vitro cellular tests and animal models suggest that M3 antagonism is considerably more important in bronchoconstriction than M2 receptor antagonism.⁵

Beta-2 receptors are the predominant adrenergic receptors in bronchial smooth muscle and, when activated, produce a subsequent relaxation of bronchial smooth muscle.⁶ Additionally, there are beta-2 receptors in the human heart, accounting for 10% to 50% of the total beta-adrenergic receptors in the body.¹ Vilanterol is a highly selective LABA that activates beta-2 adrenoreceptors on airway smooth muscle, causing bronchodilation.^{1,6,7} In vitro and in vivo, vilanterol has 24-hour activity; in vitro tests have shown similar functional selectivity to salmeterol.^{1,7-9} The functional selectivity of vilanterol is 1,000- and 400-fold more selective for beta-2 receptors than for beta-1 and beta-3 receptors, respectively.⁷ The pharmacologic effects of vilanterol are in part attributable to stimulation of intracellular adenyl cyclase, which

increases cyclic adenosine monophosphate (AMP) that then activates protein kinase A. This causes a reduction in myosin-regulatory, light-chain activity and produces bronchial smooth muscle relaxation.^{1,6} The increased cyclic AMP levels also inhibit the release of mediators of immediate hypersensitivity from cells (eg, mast cells).¹ Additionally, beta-2 agonists cause a phosphorylation of calcium-dependent potassium channels and smooth muscle relaxation, independent of its effects on protein kinase A.⁶

PHARMACOKINETICS

Following inhalation of umeclidinium and/or vilanterol, time to maximum concentration (T_{max}) occurred at a median of 5 to 15 minutes.^{1,4,7,8,10-14} There was no difference in vilanterol T_{max} when delivered as monotherapy or in combination.¹² The steady state of umeclidinium/vilanterol is achieved within 14 days, with 1.8- and 1.7-fold accumulation, respectively.¹ However, there is very little increase in maximum serum concentration from days 7 to 14.^{4,10,14} Following intravenous (IV) administration, the mean volume of distribution is 86 L for umeclidinium and 165 L for vilanterol, with an average protein binding in human plasma of 89% and 94%, respectively.¹

In vitro studies show that umeclidinium is metabolized by cytochrome P450 (CYP-450) 2D6 and is a substrate for P-glycoprotein transport.^{1,10,11} Umeclidinium is primarily metabolized via hydroxylation and O-dealkylation followed by conjugation, which results in the production of metabolites with reduced pharmacological activity.¹ In vitro studies show that vilanterol is metabolized by CYP3A4 and is a substrate for P-glycoprotein transport. Vilanterol is metabolized to a range of metabolites with significantly reduced beta-1 and beta-2 agonist activity.^{1,13}

Following IV administration of radiolabeled umeclidinium, 58% was recovered in feces and 22%

in urine. Oral dosing of radiolabeled umeclidinium resulted in recovery of 92% in feces and less than 1% in urine.^{1,10} Following oral administration of radiolabeled vilanterol, 70% was recovered in urine and 30% in feces. The effective half-life of both umeclidinium and vilanterol is 11 hours.^{1,13}

In patients with moderate hepatic impairment given umeclidinium or vilanterol, there was no increase in exposure or changes in protein binding. In patients with severe renal impairment (creatinine clearance [CrCl] less than 30 mL/min), umeclidinium exposure did not increase and vilanterol exposure increased by 56% compared with healthy patients; additionally, there were no changes in protein binding.¹

COMPARATIVE EFFICACY

Indication: Chronic Obstructive Pulmonary Disease

Guidelines

Guideline: Global Strategy for the Diagnosis, Management and Prevention of COPD

Reference: Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2013¹⁵

Comments: In patients with COPD classified as group B (forced expiratory volume in the first second of expiration [FEV₁] at least 50% predicted and/or not more than 1 exacerbation per year, Modified Medical Research Council [mMRC] dyspnea scale score of at least 2, or COPD Assessment Test [CAT] score of at least 10), group C (FEV₁ less than 50% predicted and/or at least 2 exacerbations per year, mMRC score of 0 to 1, or CAT score of less than 10), or group D (FEV₁ less than 50% predicted and/or at least 2 exacerbations per year, mMRC score of at least 2, or CAT score of at least 10), orally inhaled combination long-acting beta agonists and corticosteroids are recommended. No single combination of inhaled long-acting beta agonists and corticosteroids is preferred over another; however, long-term monotherapy with inhaled corticosteroids is not recommended, because it is less effective than combination therapy. The addition of a long-acting beta agonist to an inhaled glucocorticosteroid or tiotropium may provide additional benefits. For the treatment of acute exacerbations, short-acting beta agonists, with or without a short-acting anticholinergic, are preferred over long-acting beta agonist/inhaled corticosteroids. Umeclidinium and vilanterol, either individually or in combination, are not represented in these guidelines.

Studies

Drug: Umeclidinium/Vilanterol vs Placebo

Reference: Donohue JF, et al, 2013¹⁶

Study Design: Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study

Study Funding: GlaxoSmithKline

Patients: 1,532 patients with nonreversible COPD who are current or former cigarette smokers with a history of smoking at least 10 pack years, a post-salbutamol FEV₁/forced vital capacity (FVC) ratio of less than 0.7, a post-salbutamol FEV₁ of up to 70% of predicted normal values, and a score of 2 or higher on the mMRC dyspnea scale. Patients with asthma, other known respiratory disorders, or any uncontrolled diseases were excluded. Mean age was 62 to 64 years, 70.6% of patients were male, 49.5% were current smokers, and mean number of packs/year ranged from 45 to 47. At screening, 50.9% of patients were using inhaled corticosteroids. A stable inhaled corticosteroid dose of fluticasone propionate 1,000 mcg/day or the equivalent was allowed from 30 days prior to screening onward. At baseline, 46.2% and 42.4% of patients were GOLD stage II and stage III, respectively.

Intervention: Patients were randomized in a 3:3:3:2 ratio to receive umeclidinium 62.5 mcg, vilanterol 25 mcg, umeclidinium 62.5 mcg/vilanterol 25 mcg, or placebo once daily in the morning for 24 weeks, delivered via a dry powder inhaler. All patients received salbutamol as rescue therapy.

Results:

Primary Endpoint(s)

- The increase in mean predose trough FEV₁ at 23 and 24 hours after the dose on day 169 was 0.167 L (95% confidence interval [CI], 0.128 to 0.207 L) for umeclidinium 62.5 mcg/vilanterol 25 mcg, 0.115 L (95% CI, 0.076 to 0.155 L) for umeclidinium 62.5 mcg, and 0.072 L (95% CI, 0.032 to 0.112 L) for vilanterol 25 mcg compared with placebo ($P < .001$ for each comparison).
 - Significant increases in trough FEV₁ were observed between umeclidinium 62.5 mcg/vilanterol 25 mcg and both umeclidinium 62.5 mcg and vilanterol 25 mcg (0.052 L [95% CI, 0.017 to 0.087 L; $P = .04$] and 0.095 L [95% CI, 0.06 to 0.13 L; $P < .001$], respectively).

Secondary Endpoint(s)

- Change in 0- to 6-hour weighted mean FEV₁ at day 168 compared with placebo was 0.242 L

(95% CI, 0.202 to 0.282 L) for umeclidinium 62.5 mcg/vilanterol 25 mcg, 0.15 L (95% CI, 0.11 to 0.19 L) for umeclidinium 62.5 mcg, and 0.122 L (95% CI, 0.082 to 0.162 L) for vilanterol 25 mcg ($P < .001$ for each comparison).

- Increase from baseline with umeclidinium 62.5 mcg/vilanterol 25 mcg compared with umeclidinium 62.5 mcg was 0.092 L (95% CI, 0.056 to 0.127 L; $P < .001$), and compared with vilanterol 25 mcg was 0.12 L (95% CI, 0.084 to 0.155 L; $P < .001$).
- The proportion of patients achieving an increase in FEV₁ of at least 12% and at least 0.2 L from baseline 0 to 6 hours postdose on day 1 for umeclidinium 62.5 mcg/vilanterol 25 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo was 61%, 50%, 47%, and 15%, respectively.
- The difference from placebo peak increase in FEV₁ at day 168 was 0.224 L (95% CI, 0.182 to 0.267 L) for umeclidinium 62.5 mcg/vilanterol 25 mcg, 0.094 L (95% CI, 0.057 to 0.132 L) for umeclidinium 62.5 mcg, and 0.116 L (95% CI, 0.078 to 0.153 L) for vilanterol 25 mcg ($P < .001$, for all comparisons).
- Improvement in trough FVC from baseline at day 169 relative to placebo was as follows: umeclidinium 62.5 mcg/vilanterol 25 mcg, 0.248 L (95% CI, 0.184 to 0.313 L; $P < .001$); umeclidinium 62.5 mcg, 0.175 L (95% CI, 0.11 to 0.239 L; $P < .001$); and vilanterol 25 mcg, 0.105 L (95% CI, 0.04 to 0.17 L; $P < .01$).
- Improvement in trough FVC for umeclidinium 62.5 mcg/vilanterol 25 mcg compared with umeclidinium 62.5 mcg was 0.074 L (95% CI, 0.016 to 0.131 L; $P < .05$), and compared with vilanterol 25 mcg was 0.143 L (95% CI, 0.086 to 0.201 L; $P < .001$).
- Proportion of patients achieving an increase in trough FEV₁ of at least 0.1 L above baseline at day 169 with umeclidinium 62.5 mcg/vilanterol 25 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo was 49%, 43%, 35%, and 19%, respectively.

Endpoint(s)

- Change in mean Transition Dyspnea Index (TDI) focal score on day 169 for umeclidinium 62.5 mcg/vilanterol 25 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg compared with placebo was 1.2, 1, and 0.9, respectively ($P < .001$ for each comparison).

- Decrease in mean St. George's Respiratory Questionnaire score on day 168 was significant for umeclidinium 62.5 mcg/vilanterol 25 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg (absolute difference vs placebo; $P < .001$ for each comparison).
- The difference in mean number of salbutamol rescue therapy per day with umeclidinium 62.5 mcg/vilanterol 25 mcg and vilanterol 25 mcg compared with placebo was -0.8 and -0.9, respectively ($P < .001$ for each comparison).
- Time to first COPD exacerbation was significantly increased compared with placebo for umeclidinium 62.5 mcg/vilanterol 25 mcg (hazard ratio [HR], 0.5; 95% CI, 0.3 to 0.8; $P < .01$) and umeclidinium 62.5 mcg (HR, 0.6; 95% CI, 0.4 to 1; $P < .05$).

Comments: Umeclidinium 62.5 mcg/vilanterol 25 mcg showed improvement in lung function over each drug individually and over placebo. Umeclidinium/vilanterol is the first LAMA/LABA combination to be dosed once daily, as indicated by FEV₁ endpoints taken 23 and 24 hours after the final dose. Onset of action with umeclidinium 62.5 mcg/vilanterol 25 mcg and vilanterol 25 mcg was faster than with umeclidinium 62.5 mcg alone (27, 31, and 56 minutes, respectively). Primary treatment-emergent adverse effects were headache, nasopharyngitis, upper respiratory tract infection, and cough. Adverse effects leading to withdrawal occurred in 3% of patients treated with placebo and in 6% to 8% of patients treated with an active ingredient.

Limitations: The study did not include comparison with other LAMA/LABA products.

Reference: Celli B, et al, 2014^{17,18}

Study Design: Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study

Study Funding: GlaxoSmithKline

Patients: 1,489 patients with COPD were included; at study entry, 47% of patients were categorized as GOLD stage II and 45% as stage III. At baseline, 54% to 58% of patients had cardiovascular-related current medical conditions, and 44% to 50% were using inhaled corticosteroids.

Intervention: Patients were randomized in a 3:3:3:2 ratio to umeclidinium 125 mcg/vilanterol 25 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, or

placebo once daily for 24 weeks via dry powder inhaler.

Results:

Primary Endpoint(s)

- Difference in trough FEV₁ on day 169 with umeclidinium 125 mcg/vilanterol 25 mcg compared with umeclidinium 125 mcg was 0.079 L (95% CI, 0.046 to 0.112 L; $P < .001$), compared with vilanterol 25 mcg was 0.114 L (95% CI, 0.081 to 0.148 L; $P < .001$), and compared with placebo was 0.238 L (95% CI, 0.2 to 0.276 L; $P < .001$).

Secondary Endpoint(s)

- Difference in mean TDI focal score from 0 to 6 hours postdose on day 168 with umeclidinium 125 mcg/vilanterol 25 mcg compared with umeclidinium 125 mcg was 0.6 (95% CI, 0.2 to 1; $P = .005$), compared with vilanterol 25 mcg was 0.5 (95% CI, 0.1 to 1; $P = .01$), and compared with placebo was 1 (95% CI, 0.5 to 1.5; $P < .001$).
- Difference in weighted mean FEV₁ from 0 to 6 hours postdose on day 168 with umeclidinium 125 mcg/vilanterol 25 mcg compared with umeclidinium 125 mcg was 0.109 L (95% CI, 0.076 to 0.141 L; $P < .001$), compared with vilanterol 25 mcg was 0.142 L (95% CI, 0.109 to 0.175 L; $P < .001$), and compared with placebo was 0.287 L (95% CI, 0.25 to 0.324 L; $P < .001$).

Endpoint(s)

- The incidence of adverse events was 52% to 53% in active treatment groups and 49% with placebo. Six deaths occurred (2 in the placebo group, 2 in the umeclidinium 125 mcg group, and 2 in the vilanterol 25 mcg group), but none were considered related to study drugs; the causes of death were metastatic lung cancer (2 cases; umeclidinium 125 mcg/vilanterol 25 mcg), arteriosclerosis (placebo), pneumonia (placebo), metastatic pancreatic carcinoma (umeclidinium), and acute myocardial infarction (vilanterol).

Comments: Combination therapy results in greater improvement of FEV₁ compared with monotherapy, which is consistent with other trials in patients with COPD.^{16,19} Treatment with umeclidinium 125 mcg/vilanterol 25 mcg, umeclidinium 125 mcg, and vilanterol 25 mcg reduced use of salbutamol rescue therapy and increased health-related quality of life compared with placebo ($P \leq .004$); results were not shown.

Limitations: The dose used in this study is not the FDA-approved dosage strength (umeclidinium 62.5 mcg/vilanterol 25 mcg).

Drug: Umeclidinium/Vilanterol vs Tiotropium

Reference: Anzueto A, et al, 2013¹⁹

Study Design: Phase 3, randomized, double-blind, parallel-group, double-dummy, active-controlled study

Study Funding: GlaxoSmithKline

Patients: 843 patients with COPD in the intent-to-treat population. Mean age was 63 years and 69% of patients were male.

Intervention: Following a 7- to 10-day run-in period, patients were randomized 1:1:1:1 to receive umeclidinium 125 mcg/vilanterol 25 mcg, umeclidinium 62.5 mcg/vilanterol 25 mcg, vilanterol 25 mcg, or tiotropium 18 mcg once daily for 24 weeks via dry powder inhaler.

Results:

Primary Endpoint(s)

- Mean difference in trough FEV₁ on day 169 with umeclidinium 62.5 mcg/vilanterol 25 mcg compared with vilanterol 25 mcg was 0.09 L (95% CI, 0.039 to 0.142 L; $P < .001$), and compared with tiotropium 18 mcg was 0.09 L (95% CI, 0.039 to 0.141 L; $P < .001$). The difference with umeclidinium 125 mcg/vilanterol 25 mcg compared with vilanterol 25 mcg was 0.088 L (95% CI, 0.036 to 0.14 L; $P < .001$), and compared with tiotropium 18 mcg was 0.088 L (95% CI, 0.036 to 0.14 L; $P < .001$).

Secondary Endpoint(s)

- Weighted mean difference in FEV₁ from 0 to 6 hours postdose on day 168 with umeclidinium 62.5 mcg/vilanterol 25 mcg compared with vilanterol 25 mcg was 0.077 L (95% CI, 0.025 to 0.128; $P = .004$), and compared with tiotropium 18 mcg was 0.074 L (95% CI, 0.022 to 0.125 L; $P = .005$). The difference with umeclidinium 125 mcg/vilanterol 25 mcg compared with vilanterol 25 mcg was 0.086 L (95% CI, 0.033 to 0.138 L; $P = .001$), and compared with tiotropium 18 mcg was 0.083 L (95% CI, 0.031 to 0.134 L; $P = .002$).

Comments: The study showed improvement in trough FEV₁ with both umeclidinium/vilanterol combinations compared with vilanterol alone and tiotropium. The higher dose of umeclidinium provided no additional benefit in trough FEV₁ and weighted mean FEV₁ parameters over the umecli-

dinium 62.5 mcg/vilanterol 25 mcg dose. Improvements in trough FEV₁ and weighted mean FEV₁ were similar to other short-term studies.¹⁶ The most common adverse events were nasopharyngitis (7% to 10%) and headache (4% to 10%) across all treatment groups. Two deaths (1 in the vilanterol 25 mcg group and 1 in the umeclidinium 62.5 mcg/vilanterol 25 mcg group) were reported, but no cause was mentioned.

The product labeling indicates that the clinical development program for umeclidinium/vilanterol included two 6-month, randomized, double-blind, placebo-controlled trials; two 6-month active-controlled trials; and two 12-week crossover trials in patients with COPD. Results from all trials were not found in the medical literature but are summarized in the product labeling. The majority of patients were male, white, and had a smoking history. All 6 trials were 6 months or less in duration and assessed the impact of the study drugs on lung functions, but did not include exacerbation rates as a study endpoint.¹ The placebo-controlled trials compared umeclidinium/vilanterol with the individual components and placebo. These results are similar to those reported by Donohue et al¹⁶ and Celli et al.¹⁸ Details on the 2 active-controlled trials and the two 12-week crossover trials are not provided in the product labeling; the labeling simply states that the trials provide additional support for the efficacy of umeclidinium/vilanterol in the treatment of COPD.¹

Limitations: Results from this study are only available as an abstract.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to umeclidinium, vilanterol, or any excipients.¹

Warnings and Precautions

Long-acting beta agonists may increase the risk of asthma-related death (black box warning).¹ Umeclidinium/vilanterol is not approved for the treatment of asthma. Data are not available to determine whether the rate of death in patients with COPD is increased by umeclidinium/vilanterol.¹

Umeclidinium/vilanterol should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD.¹

Umeclidinium/vilanterol should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing a LABA due to risk of cardiovascular effects and fatalities.¹

Caution should be exercised when considering coadministration of umeclidinium/vilanterol with long-term ketoconazole or other known strong CYP3A4 inhibitors. Coadministration with a strong CYP3A4 inhibitor may result in increased cardiovascular adverse effects.¹

As with other inhaled medications, umeclidinium/vilanterol can produce paradoxical bronchospasm, which may be life-threatening.¹

Hypersensitivity reactions may occur after administration of umeclidinium/vilanterol. Anaphylactic reactions may occur in patients with severe milk protein allergy after inhalation of powder products containing lactose.¹

Beta-2 agonists, including vilanterol, can produce clinically significant cardiovascular effects, as measured by increases in pulse rate, systolic or diastolic blood pressure, and cardiac arrhythmias. Umeclidinium/vilanterol inhalation powder should be used with caution in patients with cardiovascular disorders.¹

Use umeclidinium/vilanterol with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Albuterol, a beta-2 adrenoceptor agonist, administered IV has been reported to aggravate preexisting diabetes mellitus and ketoacidosis.¹

Umeclidinium/vilanterol should be used with caution in patients with narrow-angle glaucoma.¹

Umeclidinium/vilanterol should be used with caution in patients with urinary retention (eg, prostatic hyperplasia, bladder neck obstruction).¹

Beta-adrenergic agonists, including vilanterol, may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient and does not require supplementation. Additionally, beta-agonist medications may produce transient hyperglycemia in some patients.¹

Umeclidinium/vilanterol is Pregnancy Category C. Umeclidinium and vilanterol have not been studied in pregnant women.¹

Beta agonists may interfere with uterine contractions, including those during child birth. The effects of umeclidinium and vilanterol during labor are unknown; therefore, caution is advised.¹

The safety of umeclidinium and vilanterol during breast-feeding is unknown. It is not known if either of these drugs is excreted in human milk; therefore, caution is advised.¹

Use of umeclidinium/vilanterol is not approved for use in children. The only approved indication for umeclidinium/vilanterol is COPD.¹

ADVERSE REACTIONS

In 2 placebo-controlled and 2 active-controlled trials, adverse reactions occurring at a rate of at least 1% and more frequently than with placebo included pharyngitis (2% vs less than 1%), sinusitis (1% vs less than 1%), lower respiratory tract infection (1% vs less than 1%), constipation (1% vs less than 1%), diarrhea (2% vs 1%), pain in extremity (2% vs 1%), muscle spasm (1% vs less than 1%), neck pain (1% vs less than 1%), and chest pain (1% vs less than 1%).¹

Other adverse reactions occurring at a rate of less than 1% and more frequently than with placebo include productive cough, dry mouth, dyspepsia, abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles, myocardial infarction, pruritus, rash, and conjunctivitis.¹

DRUG INTERACTIONS

Vilanterol is a substrate of CYP3A4.¹ Coadministration of ketoconazole, a potent CYP3A4 inhibitor, increases systemic exposure to vilanterol. Use caution when considering coadministration of umeclidinium/vilanterol with ketoconazole or other strong CYP3A4 inhibitors (eg, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole).¹

Use caution when administering vilanterol to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents. The effects of adrenergic agonists on the cardiovascular system may be potentiated by these agents.¹

Beta-blockers may block the pulmonary effects of respiratory beta agonists, such as vilanterol, and may also produce severe bronchospasm in patients with COPD. Patients with COPD should not normally be treated with beta-blockers; however, cardioselective beta-blockers could be administered with caution if there are no acceptable alternatives.¹

Use of nonpotassium-sparing diuretics (eg, loop or thiazide diuretics) may result in hypokalemia and can be acutely worsened by beta agonists.¹

Coadministration of umeclidinium/vilanterol with other anticholinergic-containing drugs may lead to an increase in anticholinergic adverse effects.¹

RECOMMENDED MONITORING

Spirometry should be used to assess COPD severity prior to starting any LAMA/LABA combination and then once yearly thereafter. Questionnaires such as the CAT can be performed every 2 to 3 months in addition to assessment of changes in cough, sputum, breathlessness, fatigue, activity limitation, and sleep disturbances.¹⁵

Instruct patients to monitor for signs and symptoms of acute glaucoma and worsening urinary retention and to consult a physician immediately if any signs or symptoms develop.¹

Umeclidinium/vilanterol may cause changes in potassium and blood glucose. Monitor for elevations in blood glucose and decreases in serum potassium.¹

DOSING

The recommended dose is umeclidinium 62.5 mcg/vilanterol 25 mcg as a single oral inhalation taken once daily.¹ The dose should be given at the same time every day. The maximum daily dose is 1 inhalation once daily. No dosage adjustment is required for elderly patients, patients with renal impairment, or patients with moderate hepatic impairment.¹ The dosage and administration for the inhaled combination muscarinic and beta-2 agonists are summarized in Table 2.

Patients must have a short-acting beta-2 agonist available for rescue therapy. Short-acting beta-2 agonists should not be used routinely, but instead for relief of acute symptoms. If patients' use of rescue inhalers increases, it may be a signal of deteriorating disease or acute exacerbation, and prompt medical attention is indicated. Umeclidinium/vilanterol should not be used to treat acute symptoms (eg, wheezing, bronchospasms) associated with COPD.^{1,15}

PRODUCT AVAILABILITY

Anoro Ellipta was approved for marketing in the United States on December 18, 2013.²⁰ Umeclidinium bromide/vilanterol trifenate inhalation powder is available as a disposable, light-grey and red plastic inhaler containing 2 double-foil blister strips with 7 (institutional pack only) or 30 blisters each. One

Table 2. Dosage and administration of the inhaled combination muscarinic antagonists and beta-2 agonists¹⁻³

Indication	Umeclidinium bromide/ vilanterol trifenate inhalation powder (<i>Anoro Ellipta</i>)	Ipratropium bromide/ albuterol sulfate inhalation spray (<i>Combivent Respimat</i>)	Ipratropium bromide/albuterol sulfate inhalation solution (<i>DuoNeb</i>)
COPD; maintenance therapy	1 oral inhalation of umeclidinium 62.5 mcg/ vilanterol 2.5 mcg once daily		
Bronchospasm associated with COPD in patients requiring > 1 bronchodilator		1 oral inhalation of ipratropium 20 mcg/albuterol 100 mcg 4 times daily, not to exceed 6 doses in 24 h	Oral inhalation of one 3 mL (ipratropium bromide 0.5 mg, albuterol base 2.5 mg) vial 4 times daily, not to exceed 6 doses in 24 h ^{a,b}

Note: COPD = chronic obstructive pulmonary disease.

^aMust be administered using a nebulizer.

^bPari-LC-Plus nebulizer connected to a PRONEB compressor was used in clinical trials.

strip has blisters containing umeclidinium bromide 62.5 mcg per blister, and the other strip has blisters containing vilanterol trifenate 2.5 mcg per blister.¹

The product should be stored in the unopened moisture-protective foil tray (and only removed from the tray immediately before initial use) in a dry place away from direct heat or sunlight at room temperature between 68°F and 77°F (20°C and 25°C); excursions are permitted from 59°F to 86°F (15°C to 30°C).¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

No REMS is required for umeclidinium/vilanterol.²⁰

CONCLUSION

Umeclidinium/vilanterol is the first fixed-dose combination of a LAMA and LABA. Vilanterol is already approved in combination with fluticasone furoate for the treatment of COPD. Umeclidinium and vilanterol are effective as monotherapy and show increased effectiveness as combination therapy in the treatment of COPD compared with placebo. In dose-ranging studies, umeclidinium once daily was superior to placebo in increasing trough FEV₁ and showed similar efficacy to tiotropium. Umeclidinium/vilanterol is not currently indicated to reduce exacerbations because clinical trials did not evaluate this outcome.

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