

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203975Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use the ANORO ELLIPTA inhaler safely and effectively. See full prescribing information for ANORO ELLIPTA.

ANORO ELLIPTA (umeclidinium and vilanterol inhalation powder)  
FOR ORAL INHALATION USE  
Initial U.S. Approval: 2013

### WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol. (5.1)
- The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma. (5.1)

### INDICATIONS AND USAGE

ANORO ELLIPTA is a combination of umeclidinium, an anticholinergic, and vilanterol, a long-acting beta<sub>2</sub>-adrenergic agonist (LABA), indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). (1)

Important limitations: Not indicated for the relief of acute bronchospasm or for the treatment of asthma. (1, 5.2)

### DOSAGE AND ADMINISTRATION

- For oral inhalation only. (2)
- Maintenance treatment of COPD: 1 inhalation of ANORO ELLIPTA once daily. (2)

### DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Inhaler containing 2 double-foil blister strips of powder formulation for oral inhalation. One strip contains umeclidinium 62.5 mcg per blister and the other contains vilanterol 25 mcg per blister. (3)

### CONTRAINDICATIONS

- Severe hypersensitivity to milk proteins or any ingredients. (4)

### WARNINGS AND PRECAUTIONS

- LABA increase the risk of asthma-related death. (5.1)
- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.2)

- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3)
- If paradoxical bronchospasm occurs, discontinue ANORO ELLIPTA and institute alternative therapy. (5.5)
- Use with caution in patients with cardiovascular disorders. (5.7)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.8)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a physician immediately if symptoms occur. (5.9)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a physician immediately if symptoms occur. (5.10)
- Be alert to hypokalemia and hyperglycemia. (5.11)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 1\%$  and more common than placebo) include pharyngitis, sinusitis, lower respiratory tract infection, constipation, diarrhea, pain in extremity, muscle spasms, neck pain, and chest pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Use with caution. May cause cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of vilanterol on cardiovascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)
- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of ANORO ELLIPTA with other anticholinergic-containing drugs. (7.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2013

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: ASTHMA-RELATED DEATH

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 Asthma-Related Death
- 5.2 Deterioration of Disease and Acute Episodes
- 5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta<sub>2</sub>-Agonists
- 5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors
- 5.5 Paradoxical Bronchospasm
- 5.6 Hypersensitivity Reactions
- 5.7 Cardiovascular Effects
- 5.8 Coexisting Conditions
- 5.9 Worsening of Narrow-Angle Glaucoma
- 5.10 Worsening of Urinary Retention
- 5.11 Hypokalemia and Hyperglycemia

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

#### 7 DRUG INTERACTIONS

- 7.1 Inhibitors of Cytochrome P450 3A4
- 7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants
- 7.3 Beta-Adrenergic Receptor Blocking Agents

- 7.4 Non-Potassium-Sparing Diuretics

- 7.5 Anticholinergics

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment
- 8.7 Renal Impairment

#### 10 OVERDOSAGE

- 10.1 Umeclidinium
- 10.2 Vilanterol

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### 14 CLINICAL STUDIES

- 14.1 Dose-Ranging Trials
- 14.2 Confirmatory Trials

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

### **WARNING: ASTHMA-RELATED DEATH**

**Long-acting beta<sub>2</sub>-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol, one of the active ingredients in ANORO™ ELLIPTA™ [see Warnings and Precautions (5.1)].**

**The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.**

### **1 INDICATIONS AND USAGE**

ANORO ELLIPTA is a combination anticholinergic/long-acting beta<sub>2</sub>-adrenergic agonist (anticholinergic/LABA) 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.

Important Limitations of Use: ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

### **2 DOSAGE AND ADMINISTRATION**

ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg) should be administered as 1 inhalation once daily by the orally inhaled route only.

ANORO ELLIPTA should be taken at the same time every day. Do not use ANORO ELLIPTA more than 1 time every 24 hours.

No dosage adjustment is required for geriatric patients, patients with renal impairment, or patients with moderate hepatic impairment [see *Clinical Pharmacology (12.3)*].

### **3 DOSAGE FORMS AND STRENGTHS**

Inhalation Powder. Disposable light grey and red plastic inhaler containing 2 double-foil blister strips, each with 30 blisters containing powder intended for oral inhalation only. One strip contains umeclidinium (62.5 mcg per blister), and the other strip contains vilanterol (25 mcg per blister). An institutional pack containing 7 blisters per strip is also available.

### **4 CONTRAINDICATIONS**

The use of ANORO ELLIPTA is contraindicated in patients with severe hypersensitivity to milk proteins or who have demonstrated hypersensitivity to umeclidinium, vilanterol, or any of the excipients [see *Warnings and Precautions (5.6)*, *Description (11)*].

### **5 WARNINGS AND PRECAUTIONS**

#### **5.1 Asthma-Related Death**

- Data from a large placebo-controlled trial in subjects with asthma showed that LABA may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.
- A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in ANORO ELLIPTA.
- No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with ANORO ELLIPTA has been conducted. The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established. ANORO ELLIPTA is not indicated for the treatment of asthma.

## **5.2 Deterioration of Disease and Acute Episodes**

ANORO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. ANORO ELLIPTA has not been studied in subjects with acutely deteriorating COPD. The initiation of ANORO ELLIPTA in this setting is not appropriate.

ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist.

When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta<sub>2</sub>-agonist and instruct the patient on how it should be used. Increasing inhaled, short-acting beta<sub>2</sub>-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta<sub>2</sub>-agonist becomes less effective; or the patient needs more short-acting beta<sub>2</sub>-agonist than usual, these may be markers of deterioration of disease. In this setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not appropriate in this situation.

## **5.3 Excessive Use of ANORO ELLIPTA and Use With Other Long-Acting Beta<sub>2</sub>-Agonists**

ANORO ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose

may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

#### **5.4 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors**

Caution should be exercised when considering the coadministration of ANORO ELLIPTA with long-term ketoconazole and other known strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased cardiovascular adverse effects may occur [*see Drug Interactions (7.1), Clinical Pharmacology (12.3)*].

#### **5.5 Paradoxical Bronchospasm**

As with other inhaled medicines, ANORO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with ANORO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; ANORO ELLIPTA should be discontinued immediately; and alternative therapy should be instituted.

#### **5.6 Hypersensitivity Reactions**

Hypersensitivity reactions may occur after administration of ANORO ELLIPTA. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder products containing lactose; therefore, patients with severe milk protein allergy should not use ANORO ELLIPTA [*see Contraindications (4)*].

#### **5.7 Cardiovascular Effects**

Vilanterol, like other beta<sub>2</sub>-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or symptoms [*see Clinical Pharmacology (12.2)*]. If such effects occur, ANORO ELLIPTA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown.

Therefore, ANORO ELLIPTA should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

#### **5.8 Coexisting Conditions**

ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta<sub>2</sub>-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

#### **5.9 Worsening of Narrow-Angle Glaucoma**

ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

### **5.10 Worsening of Urinary Retention**

ANORO ELLIPTA should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

### **5.11 Hypokalemia and Hyperglycemia**

Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients. In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

## **6 ADVERSE REACTIONS**

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma. *[See Boxed Warning and Warnings and Precautions (5.1).]*

The following adverse reactions are described in greater detail in other sections:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.5)]*
- Cardiovascular effects *[see Warnings and Precautions (5.7)]*
- Worsening of narrow-angle glaucoma *[see Warnings and Precautions (5.9)]*
- Worsening of urinary retention *[see Warnings and Precautions (5.10)]*

### **6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the four 6-month and the one 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

**6-Month Trials:** The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on four 6-month trials: 2 placebo-controlled trials (Trials 1 and 2; n = 1,532 and n = 1,489, respectively) and 2 active-controlled trials (Trials 3 and 4; n = 843 and n = 869, respectively). Of the 4,733 subjects, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted forced expiratory volume in 1 second (FEV<sub>1</sub>) was 48% (range: 13% to 76%), the mean post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to 109%).

Subjects received 1 dose once daily of the following: ANORO ELLIPTA, umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 62.5 mcg, vilanterol 125 mcg, vilanterol 25 mcg, active control, or placebo.

**Table 1. Adverse Reactions With ANORO ELLIPTA With ≥1% Incidence and More Common Than With Placebo in Subjects With Chronic Obstructive Pulmonary Disease**

| <b>Adverse Reaction</b>                              | <b>Placebo<br/>(n = 555)<br/>%</b> | <b>ANORO<br/>ELLIPTA<br/>(n = 842)<br/>%</b> | <b>Umeclidinium<br/>62.5 mcg<br/>(n = 418)<br/>%</b> | <b>Vilanterol<br/>25 mcg<br/>(n = 1,034)<br/>%</b> |
|--|------------------------------------|--|--|--|
| Infections and infestations                          |                                    |  |  |  |
| Pharyngitis  | <1                                 | 2  | 1  | 2  |
| Sinusitis  | <1                                 | 1  | <1   | 1  |
| Lower respiratory tract infection                    | <1                                 | 1  | <1   | <1   |
| Gastrointestinal disorders                           |                                    |  |  |  |
| Constipation   | <1                                 | 1  | <1   | <1   |
| Diarrhea   | 1                                  | 2  | <1   | 2  |
| Musculoskeletal and connective tissue disorders      |                                    |  |  |  |
| Pain in extremity                                    | 1                                  | 2  | <1   | 2  |
| Muscle spasms  | <1                                 | 1  | <1   | <1   |
| Neck pain  | <1                                 | 1  | <1   | <1   |
| General disorders and administration site conditions |                                    |  |  |  |
| Chest pain   | <1                                 | 1  | <1   | <1   |

Other adverse reactions with ANORO ELLIPTA observed with an incidence less than 1% but more common than with placebo included the following: 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.

**12-Month Trial:** In a long-term safety trial, 335 subjects were treated for up to 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and baseline characteristics of the long-term safety trial were similar to those of the placebo-controlled efficacy trials described above. Adverse reactions that occurred with a frequency of greater than or equal to 1% in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection, arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection, toothache, and diabetes mellitus.

## **7 DRUG INTERACTIONS**

### **7.1 Inhibitors of Cytochrome P450 3A4**

Vilanterol, a component of ANORO ELLIPTA, is a substrate of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to vilanterol. Caution should be exercised when considering the coadministration of ANORO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) [*see Warnings and Precautions (5.4), Clinical Pharmacology (12.3)*].

### **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

Vilanterol, like other beta<sub>2</sub>-agonists, should be administered with extreme caution 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, because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

### **7.3 Beta-Adrenergic Receptor Blocking Agents**

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, but may produce severe bronchospasm in patients with COPD. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

### **7.4 Non-Potassium-Sparing Diuretics**

The electrocardiographic changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical

significance of these effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with non-potassium-sparing diuretics.

## **7.5 Anticholinergics**

There is potential for an additive interaction with concomitantly used anticholinergic medicines. Therefore, avoid coadministration of ANORO ELLIPTA with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions* (5.9, 5.10), *Adverse Reactions* (6)].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

**Teratogenic Effects:** Pregnancy Category C. There are no adequate and well-controlled trials of ANORO ELLIPTA or its individual components, umeclidinium and vilanterol, in pregnant women. Because animal reproduction studies are not always predictive of human response, ANORO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking ANORO ELLIPTA.

**Umeclidinium:** There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits).

**Vilanterol:** There were no teratogenic effects in rats and rabbits at approximately 13,000 and 70 times, respectively, the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 450 times the MRHDID in adults (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals.

**Nonteratogenic Effects: Umeclidinium:** There were no effects on perinatal and postnatal developments in rats at approximately 80 times the MRHDID in adults (on an AUC basis at maternal subcutaneous doses up to 180 mcg/kg/day).

**Vilanterol:** There were no effects on perinatal and postnatal developments in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m<sup>2</sup> basis at maternal oral doses up to 10,000 mcg/kg/day).

### **8.2 Labor and Delivery**

There are no adequate and well-controlled human trials that have investigated the effects of ANORO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, ANORO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

### **8.3 Nursing Mothers**

**ANORO ELLIPTA:** It is not known whether ANORO ELLIPTA is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when ANORO ELLIPTA is administered to a nursing woman. Since there are no data from well-controlled human studies on the use of ANORO ELLIPTA by nursing mothers, based on the data for the individual components, a decision should be made whether to discontinue nursing or to discontinue ANORO ELLIPTA, taking into account the importance of ANORO ELLIPTA to the mother.

**Umeclidinium:** It is not known whether umeclidinium is excreted in human breast milk. However, administration to lactating rats at approximately 25 times the MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may indicate transfer of umeclidinium in milk.

**Vilanterol:** It is not known whether vilanterol is excreted in human breast milk. However, other beta<sub>2</sub>-agonists have been detected in human milk.

#### **8.4 Pediatric Use**

ANORO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric patients have not been established.

#### **8.5 Geriatric Use**

Based on available data, no adjustment of the dosage of ANORO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of ANORO ELLIPTA for COPD included 2,143 subjects aged 65 and older and, of those, 478 subjects were aged 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects.

#### **8.6 Hepatic Impairment**

Patients with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increases in  $C_{max}$  or AUC, nor did protein binding differ between subjects with moderate hepatic impairment and their healthy controls. Studies in subjects with severe hepatic impairment have not been performed [see *Clinical Pharmacology (12.3)*].

#### **8.7 Renal Impairment**

There were no significant increases in either umeclidinium or vilanterol exposure in subjects with severe renal impairment ( $CrCl < 30$  mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

### **10 OVERDOSAGE**

No case of overdose has been reported with ANORO ELLIPTA.

ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to ANORO ELLIPTA. Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together

with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdose.

### 10.1 Umeclidinium

High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

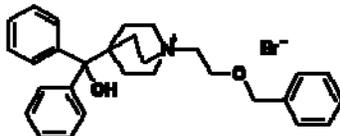
### 10.2 Vilanterol

The expected signs and symptoms with overdose of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

## 11 DESCRIPTION

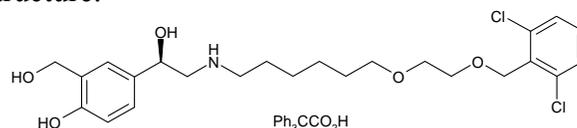
ANORO ELLIPTA is an inhalation powder drug product for delivery of a combination of umeclidinium (an anticholinergic) and vilanterol (a LABA) to patients by oral inhalation.

Umeclidinium bromide has the chemical name 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide and the following chemical structure:



Umeclidinium bromide is a white powder with a molecular weight of 508.5, and the empirical formula is  $C_{29}H_{34}NO_2 \cdot Br$  (as a quaternary ammonium bromide compound). It is slightly soluble in water.

Vilanterol trifenate has the chemical name triphenylacetic acid-4-((1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1) and the following chemical structure:



Vilanterol trifenate is a white powder with a molecular weight of 774.8, and the empirical formula is  $C_{24}H_{33}Cl_2NO_5 \cdot C_{20}H_{16}O_2$ . It is practically insoluble in water.

ANORO ELLIPTA is a light grey and red plastic inhaler containing 2 double-foil blister strips. Each blister on one strip contains a white powder mix of micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg of umeclidinium), magnesium stearate (75 mcg), and

lactose monohydrate (to 12.5 mg), and each blister on the other strip contains a white powder mix of micronized vilanterol trifenate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate (125 mcg), and lactose monohydrate (to 12.5 mg). The lactose monohydrate contains milk proteins. After the inhaler is activated, the powder within both blisters is exposed and ready for dispersion into the airstream created by the patient inhaling through the mouthpiece.

Under standardized *in vitro* test conditions, ANORO ELLIPTA delivers 55 mcg of umeclidinium and 22 mcg of vilanterol per dose when tested at a flow rate of 60 L/min for 4 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (COPD with FEV<sub>1</sub>/FVC less than 70% and FEV<sub>1</sub> less than 30% predicted or FEV<sub>1</sub> less than 50% predicted plus chronic respiratory failure), mean peak inspiratory flow through the ELLIPTA inhaler was 66.5 L/min (range: 43.5 to 81.0 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

## **12 CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of Action**

**ANORO ELLIPTA:** ANORO ELLIPTA contains both umeclidinium and vilanterol. The mechanisms of action described below for the individual components apply to ANORO ELLIPTA. These drugs represent 2 different classes of medications (an anticholinergic and a LABA) that have different effects on clinical and physiological indices.

**Umeclidinium:** Umeclidinium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine and acetylcholine-induced bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical relevance of these findings is unknown. The bronchodilation following inhalation of umeclidinium is predominantly a site-specific effect.

**Vilanterol:** Vilanterol is a LABA. *In vitro* tests have shown the functional selectivity of vilanterol was similar to salmeterol. The clinical relevance of this *in vitro* finding is unknown.

Although beta<sub>2</sub>-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta<sub>1</sub>-receptors are the predominant receptors in the heart, there are also beta<sub>2</sub>-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta<sub>2</sub>-agonists may have cardiac effects.

The pharmacologic effects of beta<sub>2</sub>-adrenergic agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic

AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

## 12.2 Pharmacodynamics

**Cardiovascular Effects: Healthy Subjects:** QTc interval prolongation was studied in a double-blind, multiple dose, placebo- and positive-controlled crossover trial in 86 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 4.6 (7.1) ms and 8.2 (10.7) ms for umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium/vilanterol 500 mcg/100 mcg (8/4 times the recommended dosage), respectively.

A dose-dependent increase in heart rate was also observed. The maximum mean (95% upper confidence bound) difference in heart rate from placebo after baseline correction was 8.8 (10.5) beats/min and 20.5 (22.3) beats/min seen 10 minutes after dosing for umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium/vilanterol 500 mcg/100 mcg, respectively.

**Chronic Obstructive Pulmonary Disease:** The effect of ANORO ELLIPTA on cardiac rhythm in subjects diagnosed with COPD was assessed using 24-hour Holter monitoring in 6- and 12-month trials: 53 subjects received ANORO ELLIPTA, 281 subjects received umeclidinium/vilanterol 125 mcg/25 mcg, and 182 subjects received placebo. No clinically meaningful effects on cardiac rhythm were observed.

## 12.3 Pharmacokinetics

Linear pharmacokinetics was observed for umeclidinium (62.5 to 500 mcg) and vilanterol (25 to 100 mcg).

**Absorption: Umeclidinium:** Umeclidinium plasma levels may not predict therapeutic effect. Following inhaled administration of umeclidinium in healthy subjects,  $C_{max}$  occurred at 5 to 15 minutes. Umeclidinium is mostly absorbed from the lung after inhaled doses with minimum contribution from oral absorption. Following repeat dosing of inhaled ANORO ELLIPTA, steady state was achieved within 14 days with up to 1.8-fold accumulation.

**Vilanterol:** Vilanterol plasma levels may not predict therapeutic effect. Following inhaled administration of vilanterol in healthy subjects,  $C_{max}$  occurred at 5 to 15 minutes. Vilanterol is mostly absorbed from the lung after inhaled doses with negligible contribution from oral absorption. Following repeat dosing of inhaled ANORO ELLIPTA, steady state was achieved within 14 days with up to 1.7-fold accumulation.

**Distribution: Umeclidinium:** Following intravenous administration to healthy subjects, the mean volume of distribution was 86 L. *In vitro* plasma protein binding in human plasma was on average 89%.

**Vilanterol:** Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165 L. *In vitro* plasma protein binding in human plasma was on average 94%.

**Metabolism: Umeclidinium:** *In vitro* data showed that umeclidinium is primarily metabolized by the enzyme cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-

glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

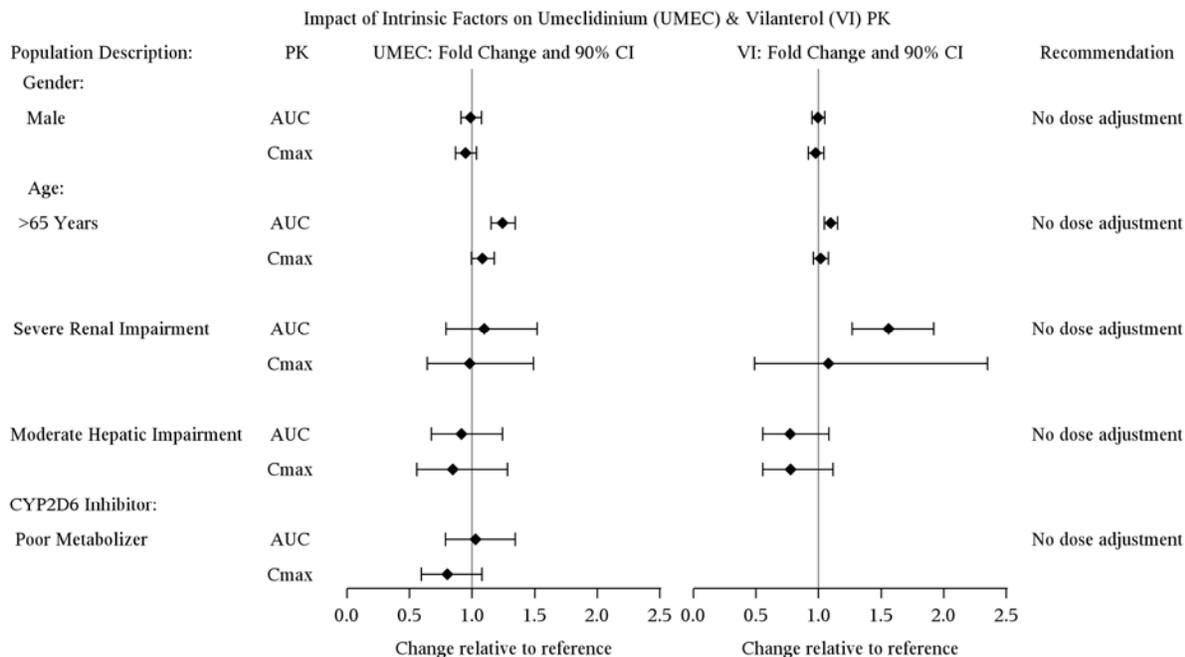
*Vilanterol:* *In vitro* data showed that vilanterol is metabolized principally by CYP3A4 and is a substrate for the P-gp transporter. Vilanterol is metabolized to a range of metabolites with significantly reduced  $\beta_1$ - and  $\beta_2$ -agonist activity.

**Elimination: Umeclidinium:** Following intravenous dosing with radio-labeled umeclidinium, mass balance showed 58% of the radio-label in the feces and 22% in the urine. The excretion of the drug-related material in the feces following intravenous dosing indicated elimination in the bile. Following oral dosing to healthy male subjects, radio-label recovered in feces was 92% of the total dose and that in urine was less than 1% of the total dose, suggesting negligible oral absorption. The effective half-life after once daily dosing is 11 hours.

*Vilanterol:* Following oral administration of radio-labeled vilanterol, mass balance showed 70% of the radio-label in the urine and 30% in the feces. The effective half-life for vilanterol, as determined from inhalation administration of multiple doses, is 11 hours.

**Special Populations:** The effects of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of umeclidinium and vilanterol are shown in Figure 1. Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age (40 to 93 years) (see Figure 1), gender (69% male) (see Figure 1), inhaled corticosteroid use (48%), or weight (34 to 161 kg) on systemic exposure of either umeclidinium or vilanterol. In addition, there was no evidence of a clinically significant effect of race.

**Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Umeclidinium and Vilanterol**



**Hepatic Impairment:** The impact of hepatic impairment on the pharmacokinetics of ANORO ELLIPTA has been evaluated in subjects with moderate hepatic impairment (Child-Pugh score of 7-9). There was no evidence of an increase in systemic exposure to either umeclidinium or vilanterol ( $C_{max}$  and AUC) (see Figure 1). There was no evidence of altered protein binding in subjects with moderate hepatic impairment compared with healthy subjects. ANORO ELLIPTA has not been evaluated in subjects with severe hepatic impairment.

**Renal Impairment:** The pharmacokinetics of ANORO ELLIPTA has been evaluated in subjects with severe renal impairment (creatinine clearance <30 mL/min). Umeclidinium systemic exposure was not increased and vilanterol systemic exposure ( $AUC_{(0-24)}$ ) was 56% higher in subjects with severe renal impairment compared with healthy subjects (see Figure 1). There was no evidence of altered protein binding in subjects with severe renal impairment compared with healthy subjects.

**Drug Interactions:** When umeclidinium and vilanterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each active substance was administered separately.

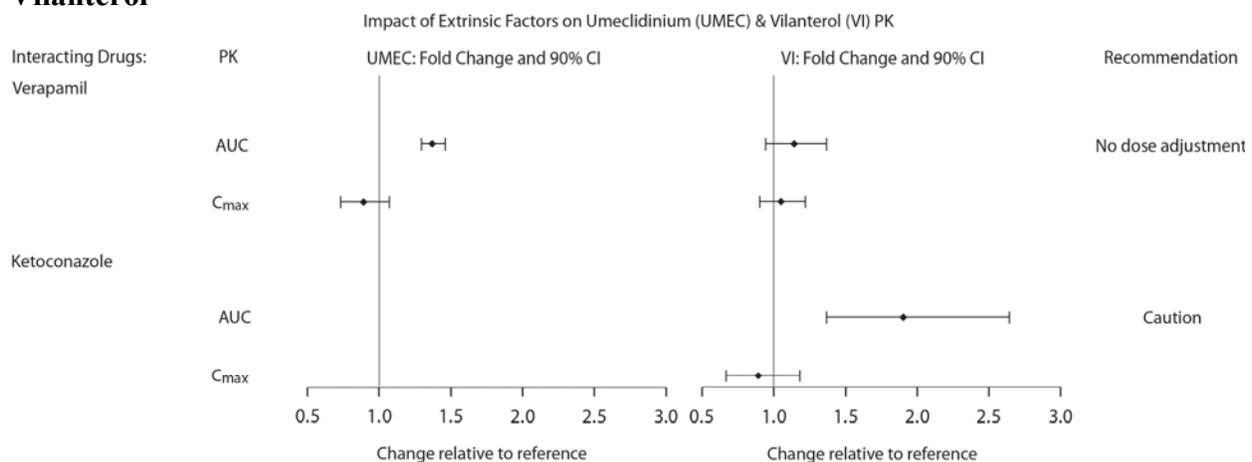
**Inhibitors of Cytochrome P450 3A4:** Vilanterol is a substrate of CYP3A4. A double-blind, repeat-dose, 2-way crossover drug interaction trial was conducted in healthy subjects to investigate the pharmacokinetic and pharmacodynamic effects of vilanterol 25 mcg as an inhalation powder with ketoconazole 400 mg. The plasma concentrations of vilanterol were higher after single and repeated doses when coadministered with ketoconazole than with placebo

(see Figure 2). The increase in vilanterol exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate or blood potassium.

**Inhibitors of P-glycoprotein Transporter:** Umeclidinium and vilanterol are both substrates of P-gp. The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy subjects. No effect on umeclidinium or vilanterol  $C_{max}$  was observed; however, an approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC (see Figure 2).

**Inhibitors of Cytochrome P450 2D6:** *In vitro* metabolism of umeclidinium is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to umeclidinium (500 mcg) (8 times the approved dose) was observed following repeat daily inhaled dosing in CYP2D6 normal (ultrarapid, extensive, and intermediate metabolizers) and poor metabolizer subjects (see Figure 1).

**Figure 2. Impact of Extrinsic Factors on the Pharmacokinetics (PK) of Umeclidinium and Vilanterol**



## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**ANORO ELLIPTA:** No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with ANORO ELLIPTA; however, studies are available for individual components, umeclidinium and vilanterol, as described below.

**Umeclidinium:** Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 mcg/kg/day and 295/200 mcg/kg/day (male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

Umeclidinium tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vitro* mouse lymphoma assay, and *in vivo* rat bone marrow micronucleus assay.

No evidence of impairment of fertility was observed in male and female rats at subcutaneous doses up to 180 mcg/kg/day and inhaled doses up to 294 mcg/kg/day, respectively (approximately 100 and 50 times, respectively, the MRHDID in adults on an AUC basis).

**Vilanterol:** In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 7,800 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 210 times the MRHDID in adults on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 1 time the MRHDID in adults on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the *in vitro* Ames assay, *in vivo* rat bone marrow micronucleus assay, *in vivo* rat unscheduled DNA synthesis (UDS) assay, and *in vitro* Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the *in vitro* mouse lymphoma assay.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,500 times, respectively, the MRHDID in adults on a mcg/m<sup>2</sup> basis).

## 14 CLINICAL STUDIES

The safety and efficacy of ANORO ELLIPTA were evaluated in a clinical development program that included 6 dose-ranging trials, 4 lung function trials of 6 months' duration (2 placebo-controlled and 2 active-controlled), two 12-week crossover trials, and a 12-month long-term safety trial. The efficacy of ANORO ELLIPTA is based primarily on the dose-ranging trials in 1,908 subjects with COPD or asthma and the 2 placebo-controlled confirmatory trials with additional support from the 2 active-controlled and 2 crossover trials in 5,388 subjects with COPD.

### 14.1 Dose-Ranging Trials

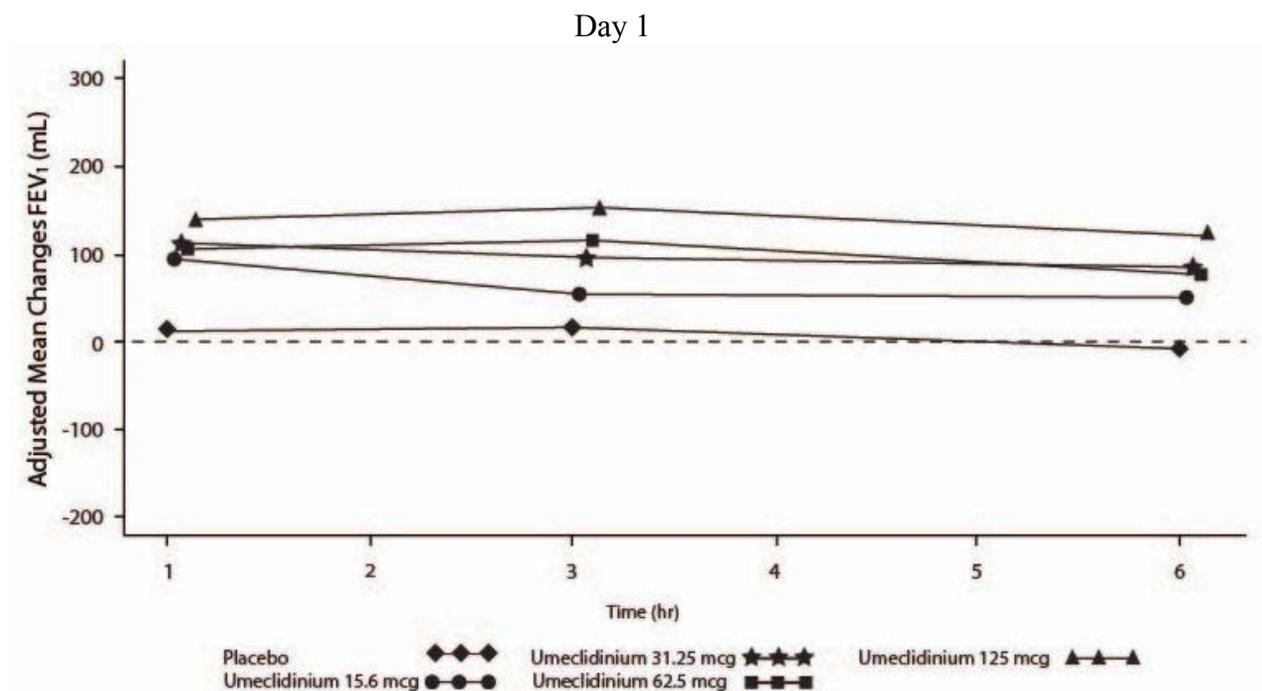
Dose selection for ANORO ELLIPTA for COPD was based on dose-ranging trials for the individual components, vilanterol and umeclidinium. Based on the findings from these studies, once-daily doses of umeclidinium/vilanterol 62.5 mcg/25 mcg and umeclidinium/vilanterol 125 mcg/25 mcg were evaluated in the confirmatory COPD trials. **ANORO ELLIPTA is not indicated for asthma.**

**Umeclidinium:** Dose selection for umeclidinium in COPD was supported by a 7-day, randomized, double-blind, placebo-controlled, crossover trial evaluating 4 doses of umeclidinium (15.6 to 125 mcg) or placebo dosed once daily in the morning in 163 subjects with COPD. A dose ordering was observed, with the 62.5- and 125-mcg doses demonstrating larger improvements in FEV<sub>1</sub> over 24 hours compared with the lower doses of 15.6 and 31.25 mcg (Figure 3).

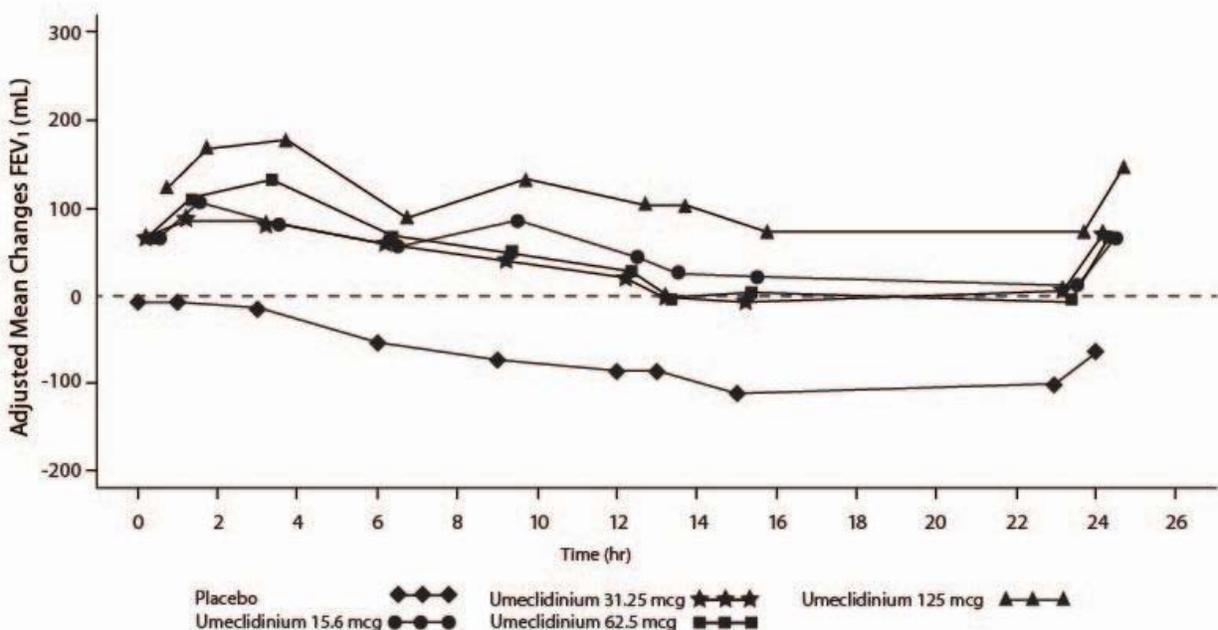
The differences in trough FEV<sub>1</sub> from baseline after 7 days for placebo and the 15.6-, 31.25-, 62.5-, and 125-mcg doses were -74 mL (95% CI: -118, -31), 38 mL (95% CI: -6, 83), 27 mL (95% CI: -18, 72), 49 mL (95% CI: 6, 93), and 109 mL (95% CI: 65, 152), respectively. Two additional dose-ranging trials in subjects with COPD demonstrated minimal additional benefit at doses above 125 mcg. The dose-ranging results supported the evaluation of 2 doses of umeclidinium, 62.5 and 125 mcg, in the confirmatory COPD trials to further assess dose response.

Evaluations of dosing interval by comparing once- and twice-daily dosing supported selection of a once-daily dosing interval for further evaluation in the confirmatory COPD trials.

**Figure 3. Adjusted Mean Change From Baseline in Post-Dose Serial FEV<sub>1</sub> (mL) on Days 1 and 7**

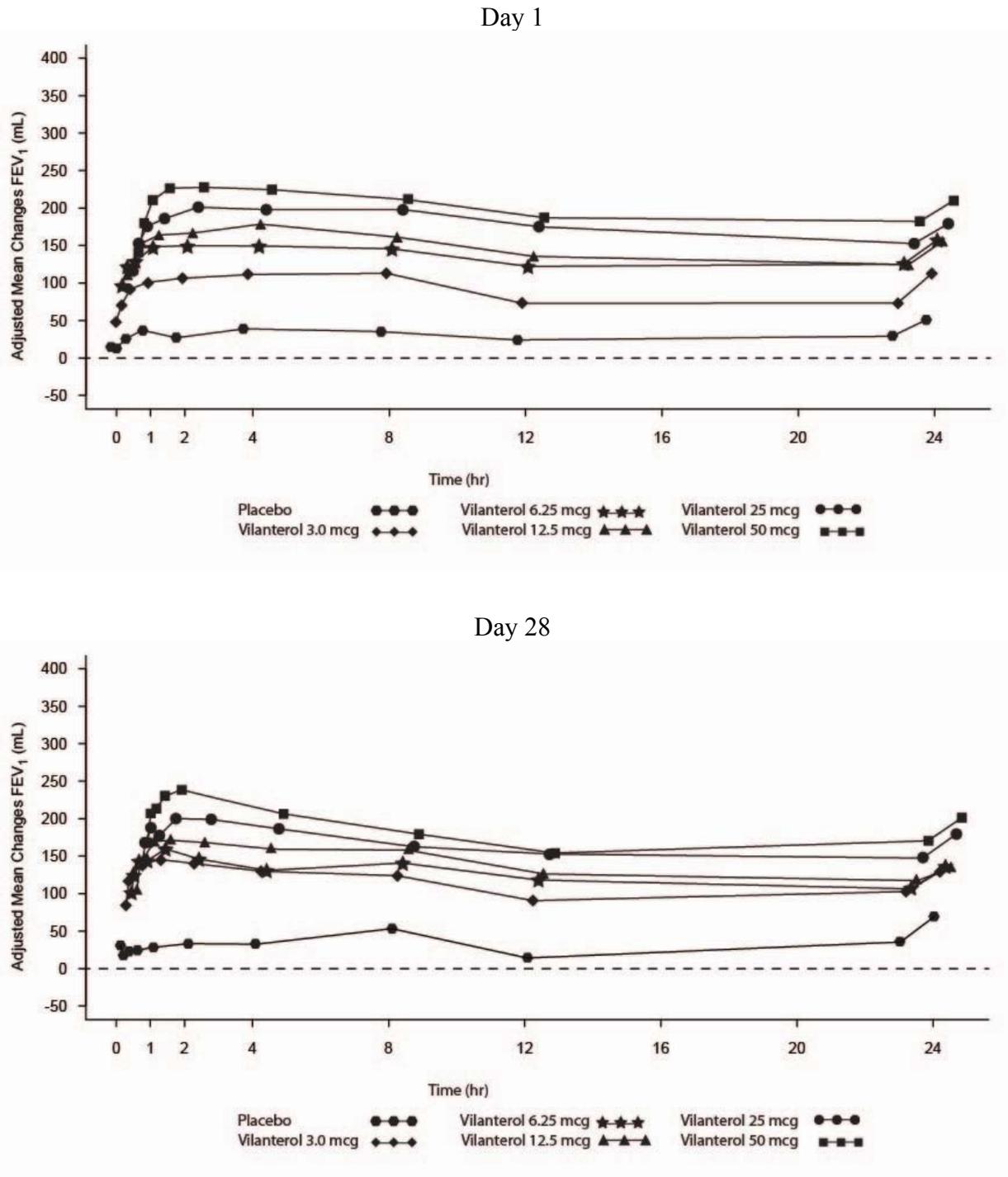


## Day 7



**Vilanterol:** Dose selection for vilanterol in COPD was supported by a 28-day, randomized, double-blind, placebo-controlled, parallel-group trial evaluating 5 doses of vilanterol (3 to 50 mcg) or placebo dosed in the morning in 602 subjects with COPD. Results demonstrated dose-related increases in FEV<sub>1</sub> compared with placebo at Day 1 and Day 28 (Figure 4).

**Figure 4. Adjusted Mean Change From Baseline in Post-Dose Serial FEV<sub>1</sub> (0-24 hr, mL) on Days 1 and 28**



The differences in trough FEV<sub>1</sub> after Day 28 from baseline for placebo and the 3-, 6.25-, 12.5-, 25-, and 50-mcg doses were 29 mL (95% CI: -8, 66), 120 mL (95% CI: 83, 158), 127 mL (95% CI: 90, 164), 138 mL (95% CI: 101, 176), 166 mL (95% CI: 129, 203), and 194 mL (95%

CI: 156, 231), respectively. These results supported the evaluation of vilanterol 25 mcg in the confirmatory COPD trials.

Dose-ranging trials in subjects with asthma evaluated doses from 3 to 50 mcg and 12.5 mcg once-daily versus 6.25 mcg twice-daily dosing frequency. The results supported the selection of the vilanterol 25 mcg once-daily dose for further evaluation in the confirmatory COPD trials.

## **14.2 Confirmatory Trials**

The clinical development program for ANORO ELLIPTA included two 6-month, randomized, double-blinded, placebo-controlled, parallel-group trials; two 6-month active-controlled trials; and two 12-week crossover trials in subjects with COPD designed to evaluate the efficacy of ANORO ELLIPTA on lung function. The 6-month trials treated 4,733 subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a post-albuterol FEV<sub>1</sub> less than or equal to 70% of predicted normal values, had a ratio of FEV<sub>1</sub>/FVC of less than 0.7, and had a Modified Medical Research Council (mMRC) score greater than or equal to 2. Of the 4,713 subjects included in the efficacy analysis, 68% were male and 84% were Caucasian. They had a mean age of 63 years and an average smoking history of 45 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted FEV<sub>1</sub> was 48% (range: 13% to 76%), the mean post-bronchodilator FEV<sub>1</sub>/FVC ratio was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -36% to 109%).

Trial 1 evaluated ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg), umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo. The primary endpoint was change from baseline in trough (predose) FEV<sub>1</sub> at Day 169 (defined as the mean of the FEV<sub>1</sub> values obtained at 23 and 24 hours after the previous dose on Day 168) compared with placebo, umeclidinium 62.5 mcg, and vilanterol 25 mcg. The comparison of ANORO ELLIPTA with umeclidinium 62.5 mcg and vilanterol 25 mcg was assessed to evaluate the contribution of the individual comparators to ANORO ELLIPTA. ANORO ELLIPTA demonstrated a larger increase in mean change from baseline in trough (predose) FEV<sub>1</sub> relative to placebo, umeclidinium 62.5 mcg, and vilanterol 25 mcg (Table 2).

**Table 2. Least Squares (LS) Mean Change From Baseline in Trough FEV<sub>1</sub> (mL) at Day 169 in the Intent-to-Treat Population (Trial 1)**

| Treatment     | n   | Trough FEV <sub>1</sub> (mL) at Day 169 |  |  |
|---------------|-----|---|--|--|
|               |     | Difference From                         |  |  |
|               |     | Placebo<br>(95% CI)<br>n = 280          | Umeclidinium<br>62.5 mcg <sup>a</sup><br>(95% CI)<br>n = 418 | Vilanterol<br>25 mcg <sup>a</sup><br>(95% CI)<br>n = 421 |
| ANORO ELLIPTA | 413 | 167<br>(128, 207)                       | 52<br>(17, 87)   | 95<br>(60, 130)  |

n = Number in intent-to-treat population.

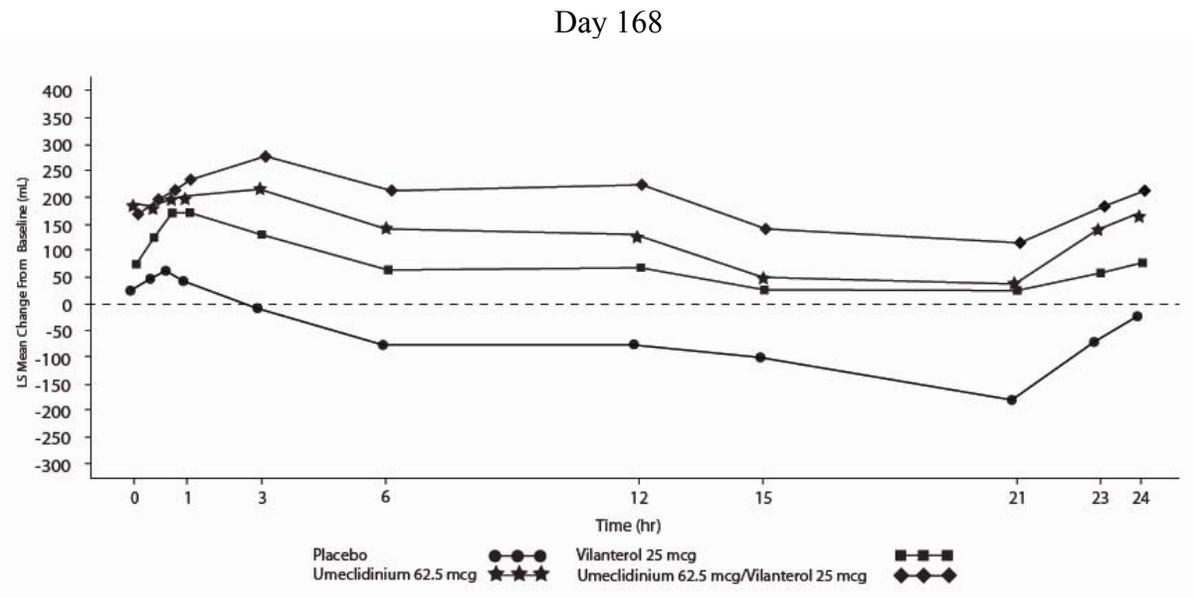
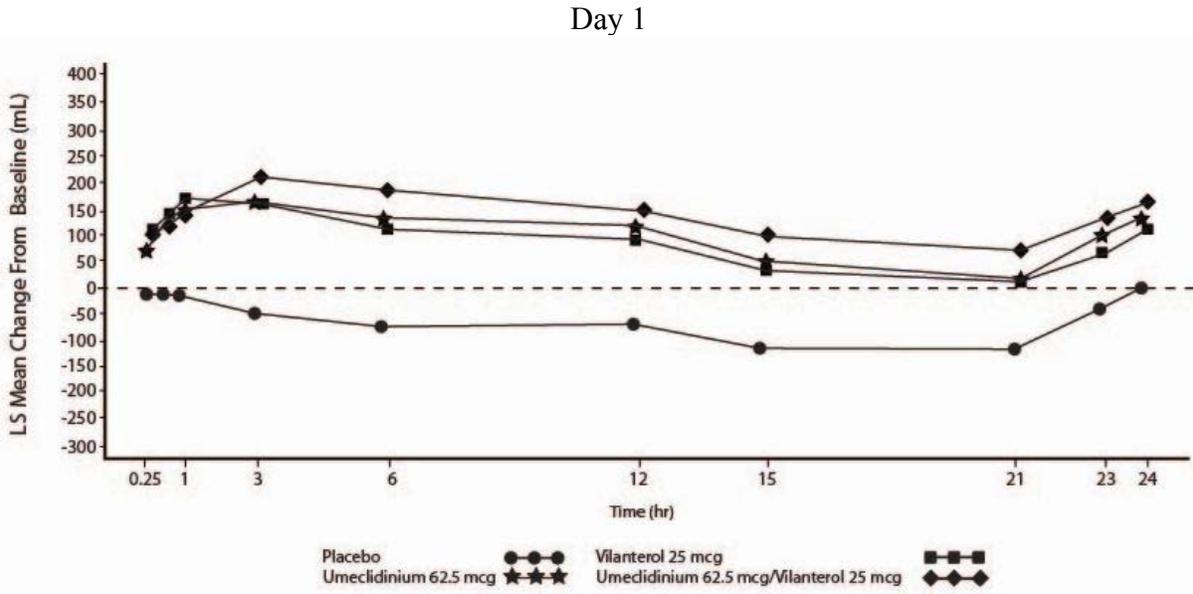
<sup>a</sup> The umeclidinium and vilanterol comparators used the same inhaler and excipients as ANORO ELLIPTA.

Trial 2 had a similar study design as Trial 1 but evaluated umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, and placebo. Results for umeclidinium/vilanterol 125 mcg/25 mcg in Trial 2 were similar to those observed for ANORO ELLIPTA in Trial 1.

Results from the two active-controlled trials and the two 12-week trials provided additional support for the efficacy of ANORO ELLIPTA in terms of change from baseline in trough FEV<sub>1</sub> compared with the single-ingredient comparators and placebo.

Serial spirometric evaluations throughout the 24-hour dosing interval were performed in a subset of subjects (n = 197) at Days 1, 84, and 168 in Trial 1. Results from Trial 1 at Day 1 and Day 168 are shown in Figure 5.

**Figure 5. Least Squares (LS) Mean Change From Baseline in FEV<sub>1</sub> (mL) Over Time (0-24 h) on Days 1 and 168 (Trial 1 Subset Population)**



The peak FEV<sub>1</sub> was defined as the maximum FEV<sub>1</sub> recorded within 6 hours after the dose of trial medicine on Days 1, 28, 84, and 168 (measurements recorded at 15 and 30 minutes and 1, 3, and 6 hours). The mean peak FEV<sub>1</sub> improvement from baseline for ANORO ELLIPTA compared with placebo at Day 1 and at Day 168 was 167 and 224 mL, respectively. The median time to onset on Day 1, defined as a 100-mL increase from baseline in FEV<sub>1</sub>, was 27 minutes in subjects receiving ANORO ELLIPTA.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ANORO ELLIPTA is supplied as a disposable light grey and red plastic inhaler containing 2 double-foil blister strips with 30 blisters each. The inhaler is packaged in a moisture-protective foil tray with a desiccant and a peelable lid (NDC 0173-0869-10).

ANORO ELLIPTA is also supplied in an institutional pack of a disposable light grey and red plastic inhaler containing 2 double-foil blister strips with 7 blisters each. The inhaler is packaged in a moisture protective foil tray with a desiccant and a peelable lid (NDC 0173-0869-06).

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

ANORO ELLIPTA should be stored inside the unopened moisture-protective foil tray and only removed from the tray immediately before initial use. Discard ANORO ELLIPTA 6 weeks after opening the foil tray or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

**Asthma-Related Death:** Inform patients that LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death. ANORO ELLIPTA is not indicated for the treatment of asthma.

**Not for Acute Symptoms:** Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise them to treat acute symptoms with a rescue inhaler such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Symptoms get worse
- Need for more inhalations than usual of their rescue inhaler

Patients should not stop therapy with ANORO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation.

**Do Not Use Additional Long-Acting Beta<sub>2</sub>-Agonists:** Instruct patients to not use other medicines containing a LABA. Patients should not use more than the recommended once-daily dose of ANORO ELLIPTA.

Instruct patients who have been taking inhaled, short-acting beta<sub>2</sub>-agonists on a regular basis to discontinue the regular use of these products and use them only for the symptomatic relief of acute symptoms.

**Paradoxical Bronchospasm:** As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA.

**Risks Associated With Beta-Agonist Therapy:** Inform patients of adverse effects associated with beta<sub>2</sub>-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

**Worsening of Narrow-Angle Glaucoma:** Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

**Worsening of Urinary Retention:** Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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ANORO ELLIPTA was developed in collaboration with  **Theravance**.



GlaxoSmithKline  
Research Triangle Park, NC 27709

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ANR:1PI

## MEDICATION GUIDE

### **ANORO™ [*a-nor' oh*] ELLIPTA™ (umeclidinium and vilanterol inhalation powder)**

Read the Medication Guide that comes with ANORO ELLIPTA before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

### **What is the most important information I should know about ANORO ELLIPTA?**

**ANORO ELLIPTA is only approved for use in chronic obstructive pulmonary disease (COPD). ANORO ELLIPTA is NOT approved for use in asthma.**

**ANORO ELLIPTA can cause serious side effects, including:**

- **People with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines, such as vilanterol (one of the medicines in ANORO ELLIPTA), have an increased risk of death from asthma problems.**
- **It is not known if LABA medicines, such as vilanterol (one of the medicines in ANORO ELLIPTA), increase the risk of death in people with COPD.**
- **Call your healthcare provider if breathing problems worsen over time while using ANORO ELLIPTA.** You may need different treatment.
- **Get emergency medical care if:**
  - your breathing problems worsen quickly
  - you use your rescue inhaler, but it does not relieve your breathing problems.

### **What is ANORO ELLIPTA?**

ANORO ELLIPTA combines an anticholinergic, umeclidinium, and a LABA medicine, vilanterol.

Anticholinergic and LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent symptoms such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.

ANORO ELLIPTA is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. ANORO ELLIPTA is used long term as 1 inhalation, 1 time each day, to improve symptoms of COPD for better breathing.

- **ANORO ELLIPTA is not for use to treat sudden symptoms of COPD.** Always have a rescue inhaler (an inhaled, short-acting bronchodilator) with you to treat sudden symptoms. If you do not have a rescue inhaler, contact your healthcare provider to have one prescribed for you.
- **ANORO ELLIPTA is not for the treatment of asthma. It is not known if ANORO ELLIPTA is safe and effective in people with asthma.**
- ANORO ELLIPTA should not be used in children. It is not known if ANORO ELLIPTA is safe and effective in children.

### **Who should not use ANORO ELLIPTA?**

Do not use ANORO ELLIPTA if you:

- have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- are allergic to umeclidinium, vilanterol, or any of the ingredients in ANORO ELLIPTA. See “What are the ingredients in ANORO ELLIPTA?” below for a complete list of ingredients.

### **What should I tell my healthcare provider before using ANORO ELLIPTA?**

**Tell your healthcare provider about all of your health conditions, including if you:**

- have heart problems
- have high blood pressure
- have seizures
- have thyroid problems
- have diabetes
- have liver problems
- have eye problems such as glaucoma. ANORO ELLIPTA may make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. ANORO ELLIPTA may make these problems worse.
- are allergic to any of the ingredients in ANORO ELLIPTA, any other medicines, or food products. See “What are the ingredients in ANORO ELLIPTA?” below for a complete list of ingredients.
- have any other medical conditions
- are pregnant or planning to become pregnant. It is not known if ANORO ELLIPTA may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in ANORO ELLIPTA pass into your milk and if they can harm your baby.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ANORO ELLIPTA and certain other medicines may interact with each other. This may cause serious side effects.

Especially tell your healthcare provider if you take:

- anticholinergics (including tiotropium, ipratropium, aclidinium)
- atropine

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

### **How should I use ANORO ELLIPTA?**

**Read the step-by-step instructions for using ANORO ELLIPTA at the end of this Medication Guide.**

- **Do not** use ANORO ELLIPTA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- Use ANORO ELLIPTA exactly as your healthcare provider tells you to use it. **Do not** use ANORO ELLIPTA more often than prescribed.
- Use 1 inhalation of ANORO ELLIPTA 1 time each day. Use ANORO ELLIPTA at the same time each day.
- If you miss a dose of ANORO ELLIPTA, take it as soon as you remember. Do not take more than 1 inhalation each day. Take your next dose at your usual time. Do not take 2 doses at one time.
- If you take too much ANORO ELLIPTA, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA or an anticholinergic for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA or anticholinergic medicines.
- Do not stop using ANORO ELLIPTA unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **ANORO ELLIPTA does not relieve sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse
  - you need to use your rescue inhaler more often than usual
  - your rescue inhaler does not work as well to relieve your symptoms

**What are the possible side effects with ANORO ELLIPTA?**

**ANORO ELLIPTA can cause serious side effects, including:**

- **See “What is the most important information I should know about ANORO ELLIPTA?”**
- **sudden breathing problems immediately after inhaling your medicine**

- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of the face, mouth, and tongue
  - breathing problems
- **effects on your heart**
  - increased blood pressure
  - a fast and/or irregular heartbeat
  - chest pain
- **effects on your nervous system**
  - tremor
  - nervousness
- **new or worsened eye problems including acute narrow-angle glaucoma.** Acute narrow-angle glaucoma can cause permanent loss of vision if not treated. Symptoms of acute narrow-angle glaucoma may include:
  - eye pain or discomfort
  - nausea or vomiting
  - blurred vision
  - seeing halos or bright colors around lights
  - red eyes

If you have these symptoms, call your doctor right away before taking another dose.

- **urinary retention.** People who take ANORO ELLIPTA may develop new or worse urinary retention. Symptoms of urinary retention may include:
  - difficulty urinating
  - painful urination
  - urinating frequently
  - urination in a weak stream or drips

If you have these symptoms of urinary retention, stop taking ANORO ELLIPTA and call your doctor right away before taking another dose.

- **changes in laboratory blood levels,** including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia)

**Common side effects of ANORO ELLIPTA include:**

- sore throat
- sinus infection

- lower respiratory infection
- common cold symptoms
- constipation
- diarrhea
- pain in your arms or legs
- muscle spasms
- neck pain
- chest pain

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with ANORO ELLIPTA. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How do I store ANORO ELLIPTA?**

- Store ANORO ELLIPTA at room temperature between 68°F and 77°F (20°C and 25°C). Keep in a dry place away from heat and sunlight.
- Store ANORO ELLIPTA in the unopened foil tray and only open when ready for use.
- Safely throw away ANORO ELLIPTA in the trash 6 weeks after you open the foil tray or when the counter reads "0", whichever comes first. Write the date you open the tray on the label on the inhaler.
- **Keep ANORO ELLIPTA and all medicines out of the reach of children.**

### **General information about ANORO ELLIPTA**

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use ANORO ELLIPTA for a condition for which it was not prescribed. Do not give your ANORO ELLIPTA to other people, even if they have the same condition that you have. It may harm them.

This Medication Guide summarizes the most important information about ANORO ELLIPTA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about ANORO ELLIPTA that was written for healthcare professionals.

For more information about ANORO ELLIPTA, call 1-888-825-5249 or visit our website at [www.myANORO.com](http://www.myANORO.com).

## What are the ingredients in ANORO ELLIPTA?

Active ingredients: umeclidinium, vilanterol

Inactive ingredients: lactose monohydrate (contains milk proteins), magnesium stearate

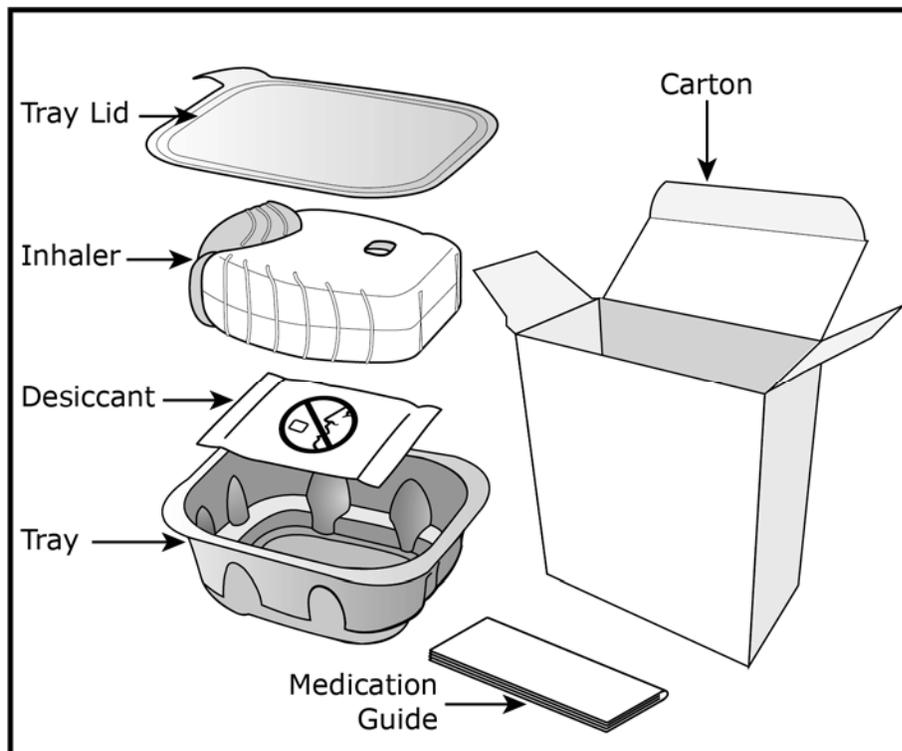
## Instructions for Use

### For Oral Inhalation Only.

#### Read this before you start:

- If you open and close the cover without inhaling the medicine, you will lose the dose.
- The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.
- It is not possible to accidentally take a double dose or an extra dose in one inhalation.

#### Your ANORO ELLIPTA inhaler



#### How to use your inhaler

- ANORO ELLIPTA comes in a foil tray.
- Peel back the lid to open the tray. See Figure A.
- The tray contains a desiccant to reduce moisture. Do not eat or inhale. Throw it away in the household trash out of reach of children and pets. See Figure B.

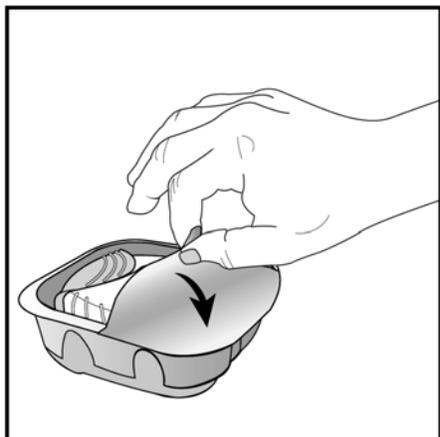


Figure A

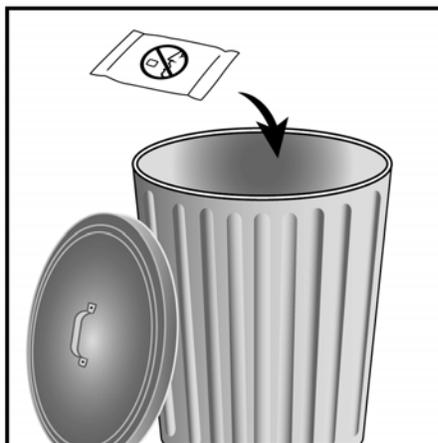


Figure B

### Important Notes:

- Your inhaler contains 30 doses (7 doses if you have a sample or institutional pack).
- Each time you open the cover of the inhaler fully (you will hear a clicking sound), a dose is ready to be inhaled. This is shown by a decrease in the number on the counter.
- If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled. It is not possible to accidentally take a double dose or an extra dose in one inhalation.
- **Do not** open the cover of the inhaler until you are ready to use it. To avoid wasting doses after the inhaler is ready, **do not** close the cover until after you have inhaled the medicine.
- Write the "Tray opened" and "Discard" dates on the inhaler label. The "Discard" date is 6 weeks from the date you open the tray.

**Check the counter. See Figure C.**

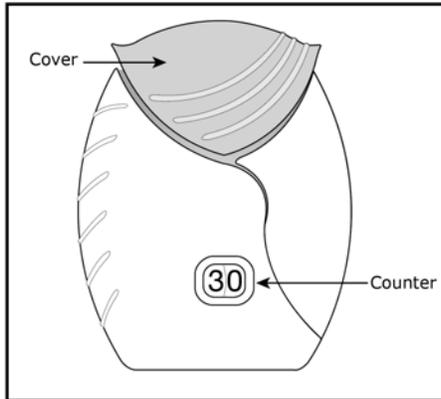


Figure C

- Before the inhaler is used for the first time, the counter should show the number 30 (7 if you have a sample or institutional pack). This is the number of doses in the inhaler.
- Each time you open the cover, you prepare 1 dose of medicine.
- The counter counts down by 1 each time you open the cover.

**Prepare your dose:**

**Wait to open the cover until you are ready to take your dose.**

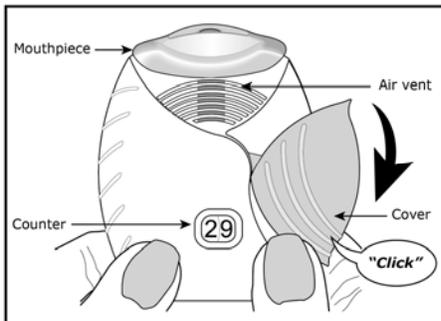


Figure D

**Step 1. Open the cover of the inhaler. See Figure D.**

- Slide the cover down to expose the mouthpiece. You should hear a “click.” The counter will count down by 1 number. You do not need to shake this kind of inhaler. **Your inhaler is now ready to use.**
- If the counter does not count down as you hear the click, the inhaler will not deliver the medicine. Call your healthcare provider or pharmacist if this happens.

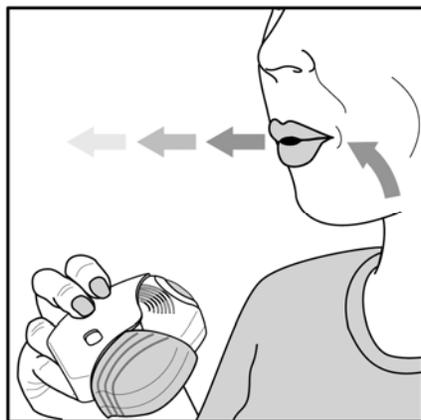
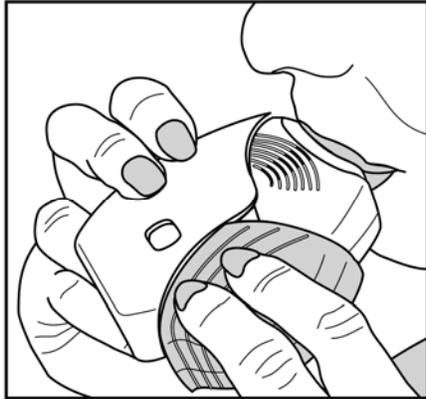


Figure E

**Step 2. Breathe out. See Figure E.**

- While holding the inhaler away from your mouth, breathe out (exhale) fully. Do not breathe out into the mouthpiece.



**Figure F**

**Step 3. Inhale your medicine. See Figure F.**

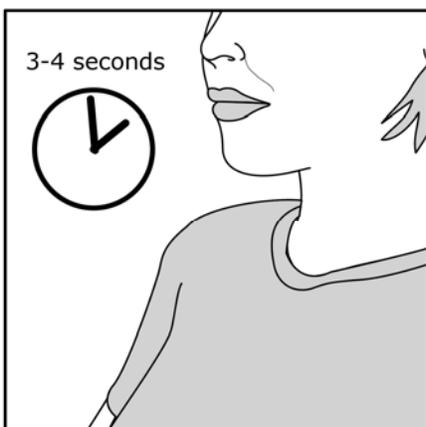
- Put the mouthpiece between your lips, and close your lips firmly around it. Your lips should fit over the curved shape of the mouthpiece.
- Take one long, steady, deep breath in through your mouth. **Do not** breathe in through your nose.

Do not block the air vent with your fingers.



**Figure G**

- Do not block the air vent with your fingers. See **Figure G**.



**Figure H**

- **Remove the inhaler from your mouth and hold your breath for about 3 to 4 seconds** (or as long as comfortable for you). See **Figure H**.

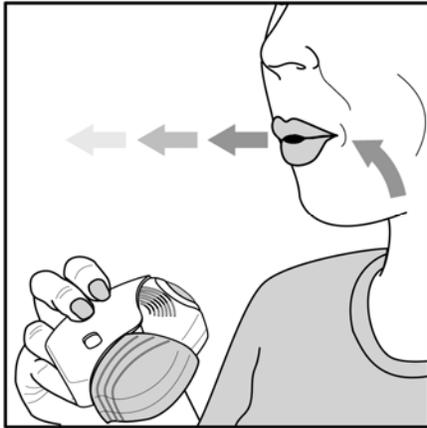


Figure I

**Step 4. Breathe out slowly and gently. See Figure I.**

- You may not taste or feel the medicine, even when you are using the inhaler correctly.
- **Do not** take another dose from the inhaler even if you do not feel or taste the medicine.

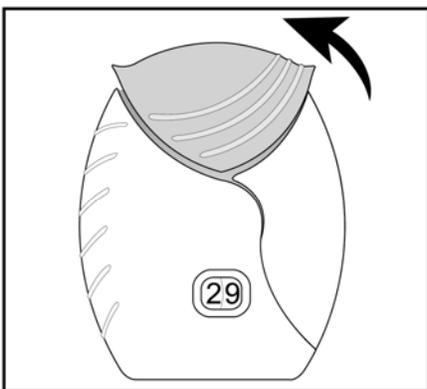


Figure J

**Step 5. Close the inhaler. See Figure J.**

- You can clean the mouthpiece if needed, using a dry tissue, before you close the cover. Routine cleaning is not required.
- Slide the cover up and over the mouthpiece as far as it will go.

**Important Note: When should you get a refill?**

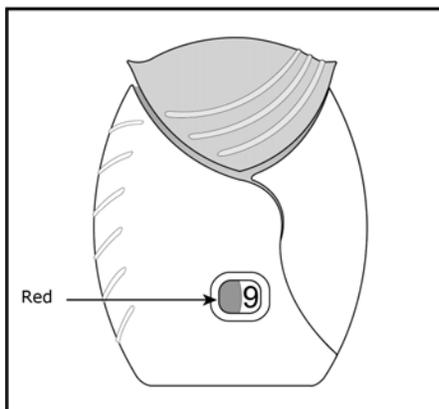


Figure K

- **When you have less than 10 doses remaining** in your inhaler, the left half of the counter shows red as a reminder to get a refill. **See Figure K.**
- After you have inhaled the last dose, the counter will show "0" and will be empty.
- Throw the empty inhaler away in your household trash out of reach of children and pets.

If you have questions about ANORO ELLIPTA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit [www.myANORO.com](http://www.myANORO.com).

**This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.**

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ANORO ELLIPTA was developed in collaboration with  **Theravance** .



GlaxoSmithKline  
Research Triangle Park, NC 27709

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December 2013

ANR: 1MG

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CURTIS J ROSEBRAUGH  
12/18/2013