

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANORO ELLIPTA 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

RECENT MAJOR CHANGES

Boxed Warning	Removed-5/2019
Indications and Usage (1)	6/2019
Contraindications (4)	5/2019
Warnings and Precautions, Serious Asthma-Related Events—Hospitalizations, Intubations, Death (5.1)	5/2019
Warnings and Precautions, Cardiovascular Effects (5.7)	6/2019

INDICATIONS AND USAGE

ANORO ELLIPTA is a combination of umeclidinium, an anticholinergic, and vilanterol, a long-acting beta₂-adrenergic agonist (LABA), indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). (1)

Important limitations of use: Not indicated for 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 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)
- Use of a LABA, including ANORO ELLIPTA, without an inhaled corticosteroid is contraindicated in patients with asthma. (4)

WARNINGS AND PRECAUTIONS

- LABA as monotherapy (without an inhaled corticosteroid) for asthma increase the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating COPD. Do not use to treat acute symptoms. (5.2)

- Do not use in combination with an additional medicine containing a 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 because of beta-adrenergic stimulation. (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 healthcare provider 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 healthcare provider 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) are 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.

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 FDA-approved patient labeling.

Revised: 6/2019

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

3 ANORO ELLIPTA is indicated for the maintenance treatment of patients with chronic
4 obstructive pulmonary disease (COPD).

5 Important Limitations of Use

6 ANORO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of
7 asthma. The safety and efficacy of ANORO ELLIPTA in asthma have not been established.

8 2 DOSAGE AND ADMINISTRATION

9 ANORO ELLIPTA (umeclidinium/vilanterol 62.5 mcg/25 mcg) should be administered as
10 1 inhalation once daily by the orally inhaled route only.

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

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

15 3 DOSAGE FORMS AND STRENGTHS

16 Inhalation powder: Disposable light grey and red plastic inhaler containing 2 foil blister strips of
17 powder intended for oral inhalation only. One strip contains umeclidinium (62.5 mcg per blister),
18 and the other strip contains vilanterol (25 mcg per blister).

19 4 CONTRAINDICATIONS

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

23 Use of a long-acting beta₂-adrenergic agonist (LABA) without an inhaled corticosteroid (ICS) is
24 contraindicated in patients with asthma [*see Warnings and Precautions (5.1)*]. ANORO
25 ELLIPTA is not indicated for the treatment of asthma.

26 5 WARNINGS AND PRECAUTIONS

27 5.1 Serious Asthma-Related Events—Hospitalizations, Intubations, Death

28 The safety and efficacy of ANORO ELLIPTA in patients with asthma have not been established.
29 ANORO ELLIPTA is not indicated for the treatment of asthma [*see Contraindications (4)*].

30 Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of
31 asthma-related death. Available data from controlled clinical trials also suggest that use of

32 LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and
33 adolescent patients. These findings are considered a class effect of LABA monotherapy. When
34 LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a
35 significant increase in the risk of serious asthma-related events (hospitalizations, intubations,
36 death) compared with ICS alone.

37 A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol)
38 with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths
39 in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in
40 subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of
41 asthma-related death is considered a class effect of LABA, including vilanterol, one of the active
42 ingredients in ANORO ELLIPTA.

43 No trial adequate to determine whether the rate of asthma-related death is increased in subjects
44 treated with ANORO ELLIPTA has been conducted.

45 Available data do not suggest an increased risk of death with use of LABA in patients with
46 COPD.

47 **5.2 Deterioration of Disease and Acute Episodes**

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

52 ANORO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy
53 for the treatment of acute episodes of bronchospasm. ANORO ELLIPTA has not been studied in
54 the relief of acute symptoms and extra doses should not be used for that purpose. Acute
55 symptoms should be treated with an inhaled, short-acting beta₂-agonist.

56 When beginning treatment with ANORO ELLIPTA, patients who have been taking oral or
57 inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to
58 discontinue the regular use of these drugs and to use them only for symptomatic relief of acute
59 respiratory symptoms. When prescribing ANORO ELLIPTA, the healthcare provider should also
60 prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used.
61 Increasing inhaled, short-acting beta₂-agonist use is a signal of deteriorating disease for which
62 prompt medical attention is indicated.

63 COPD may deteriorate acutely over a period of hours or chronically over several days or longer.
64 If ANORO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled,
65 short-acting beta₂-agonist becomes less effective; or the patient needs more short-acting
66 beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting a
67 reevaluation of the patient and the COPD treatment regimen should be undertaken at once.

68 Increasing the daily dose of ANORO ELLIPTA beyond the recommended dose is not
69 appropriate in this situation.

70 **5.3 Excessive Use of ANORO ELLIPTA and Use with Other Long-acting Beta₂-agonists**

71 ANORO ELLIPTA should not be used more often than recommended, at higher doses than
72 recommended, or in conjunction with other medicines containing LABA, as an overdose may
73 result. Clinically significant cardiovascular effects and fatalities have been reported in
74 association with excessive use of inhaled sympathomimetic drugs. Patients using ANORO
75 ELLIPTA should not use another medicine containing a LABA (e.g., salmeterol, formoterol
76 fumarate, arformoterol tartrate, indacaterol) for any reason.

77 **5.4 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors**

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

83 **5.5 Paradoxical Bronchospasm**

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

89 **5.6 Hypersensitivity Reactions**

90 Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after
91 administration of ANORO ELLIPTA. Discontinue ANORO ELLIPTA if such reactions occur.
92 There have been reports of anaphylactic reactions in patients with severe milk protein allergy
93 after inhalation of other powder medications containing lactose; therefore, patients with severe
94 milk protein allergy should not use ANORO ELLIPTA [*see Contraindications (4)*].

95 **5.7 Cardiovascular Effects**

96 Vilanterol, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in
97 some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, or
98 symptoms [*see Clinical Pharmacology (12.2)*]. If such effects occur, ANORO ELLIPTA may
99 need to be discontinued. In addition, beta-agonists have been reported to produce
100 electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval,
101 and ST segment depression, although the clinical significance of these findings is unknown.
102 Fatalities have been reported in association with excessive use of inhaled sympathomimetic
103 drugs.

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

106 In a 52-week trial of subjects with COPD, the exposure-adjusted rates for any on-treatment
107 major adverse cardiac event, including non-fatal central nervous system hemorrhages and
108 cerebrovascular conditions, non-fatal myocardial infarction, non-fatal acute myocardial
109 infarction, and adjudicated on-treatment death due to cardiovascular events, was 2.2 per
110 100 patient-years for fluticasone furoate/umeclidinium/vilanterol 100 mcg/62.5 mcg/100 mcg
111 (n = 4,151), 1.9 per 100 patient-years for fluticasone furoate/vilanterol 100 mcg/25 mcg
112 (n = 4,134), and 2.2 per 100 patient-years for ANORO ELLIPTA (n = 2,070). Adjudicated
113 on-treatment deaths due to cardiovascular events occurred in 20 of 4,151 patients (0.54 per
114 100 patient-years) receiving fluticasone furoate/umeclidinium/vilanterol, 27 of 4,134 patients
115 (0.78 per 100 patient-years) receiving fluticasone furoate/vilanterol, and 16 of 2,070 patients
116 (0.94 per 100 patient-years) receiving ANORO ELLIPTA.

117 **5.8 Coexisting Conditions**

118 ANORO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with
119 caution in patients with convulsive disorders or thyrotoxicosis and in those who are unusually
120 responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor agonist
121 albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes
122 mellitus and ketoacidosis.

123 **5.9 Worsening of Narrow-Angle Glaucoma**

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

129 **5.10 Worsening of Urinary Retention**

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

135 **5.11 Hypokalemia and Hyperglycemia**

136 Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients,
137 possibly through intracellular shunting, which has the potential to produce adverse
138 cardiovascular effects. The decrease in serum potassium is usually transient, not requiring
139 supplementation. Beta-agonist medicines may produce transient hyperglycemia in some patients.

140 In 4 clinical trials of 6-month duration evaluating ANORO ELLIPTA in subjects with COPD,
141 there was no evidence of a treatment effect on serum glucose or potassium.

142 **6 ADVERSE REACTIONS**

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

- 144 • Serious asthma-related events—hospitalizations, intubations, death. LABA, such as vilanterol
145 (one of the active ingredients in ANORO ELLIPTA), as monotherapy (without ICS) for
146 asthma increase the risk of asthma-related events. ANORO ELLIPTA is not indicated for the
147 treatment of asthma [*see Warnings and Precautions (5.1)*].
- 148 • Paradoxical bronchospasm [*see Warnings and Precautions (5.5)*]
- 149 • Cardiovascular effects [*see Warnings and Precautions (5.7)*]
- 150 • Worsening of narrow-angle glaucoma [*see Warnings and Precautions (5.9)*]
- 151 • Worsening of urinary retention [*see Warnings and Precautions (5.10)*]

152 **6.1 Clinical Trials Experience**

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

156 The clinical program for ANORO ELLIPTA included 8,138 subjects with COPD in four
157 6-month lung function trials, one 12-month long-term safety study, and 9 other trials of shorter
158 duration. A total of 1,124 subjects have received at least 1 dose of ANORO ELLIPTA
159 (umeclidinium/vilanterol 62.5 mcg/25 mcg), and 1,330 subjects have received a higher dose of
160 umeclidinium/vilanterol (125 mcg/25 mcg). The safety data described below are based on the
161 four 6-month and two 12-month trials. Adverse reactions observed in the other trials were similar
162 to those observed in the confirmatory trials.

163 6-Month Trials

164 The incidence of adverse reactions associated with ANORO ELLIPTA in Table 1 is based on
165 four 6-month trials: 2 placebo-controlled trials (Trial 1, NCT #01313650 and Trial 2,
166 NCT #01313637); N = 1,532 and N = 1,489, respectively) and 2 active-controlled trials (Trial 3,
167 NCT #01316900 and Trial 4, NCT #01316913); N = 843 and N = 869, respectively). Of the
168 4,733 subjects, 68% were male and 84% were white. They had a mean age of 63 years and an
169 average smoking history of 45 pack-years, with 50% identified as current smokers. At screening,
170 the mean postbronchodilator percent predicted forced expiratory volume in 1 second (FEV₁) was
171 48% (range: 13% to 76%), the mean postbronchodilator FEV₁/forced vital capacity (FVC) ratio
172 was 0.47 (range: 0.13 to 0.78), and the mean percent reversibility was 14% (range: -45% to
173 109%).

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

177 **Table 1. Adverse Reactions with ANORO ELLIPTA with $\geq 1\%$ Incidence and More**
 178 **Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease**

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

179 Other adverse reactions with ANORO ELLIPTA observed with an incidence <1% but more
 180 common than placebo included the following: productive cough, dry mouth, dyspepsia,
 181 abdominal pain, gastroesophageal reflux disease, vomiting, musculoskeletal chest pain, chest
 182 discomfort, asthenia, atrial fibrillation, ventricular extrasystoles, supraventricular extrasystoles,
 183 myocardial infarction, pruritus, rash, and conjunctivitis.

184 12-Month Trials

185 In a long-term safety trial (Trial 5, NCT #01316887), 335 subjects were treated for up to
 186 12 months with umeclidinium/vilanterol 125 mcg/25 mcg or placebo. The demographic and
 187 baseline characteristics of the long-term safety trial were similar to those of the
 188 placebo-controlled efficacy trials described above. Adverse reactions observed with a frequency
 189 of $\geq 1\%$ in the group receiving umeclidinium/vilanterol 125 mcg/25 mcg that exceeded that in
 190 placebo in this trial were: headache, back pain, sinusitis, cough, urinary tract infection,

191 arthralgia, nausea, vertigo, abdominal pain, pleuritic pain, viral respiratory tract infection,
192 toothache, and diabetes mellitus.

193 **6.2 Postmarketing Experience**

194 In addition to adverse reactions reported from clinical trials, the following adverse reactions have
195 been identified during postapproval use of ANORO ELLIPTA. Because these reactions are
196 reported voluntarily from a population of uncertain size, it is not always possible to reliably
197 estimate their frequency or establish a causal relationship to drug exposure. These events have
198 been chosen for inclusion due to either their seriousness, frequency of reporting, or causal
199 connection to ANORO ELLIPTA or a combination of these factors.

200 Cardiac Disorders

201 Palpitations.

202 Eye Disorders

203 Blurred vision, glaucoma, increased intraocular pressure.

204 Immune System Disorders

205 Hypersensitivity reactions, including anaphylaxis, angioedema, and urticaria.

206 Nervous System Disorders

207 Dysgeusia, tremor.

208 Psychiatric Disorders

209 Anxiety.

210 Renal and Urinary Disorders

211 Dysuria, urinary retention.

212 Respiratory, Thoracic, and Mediastinal Disorders

213 Dysphonia, paradoxical bronchospasm.

214 **7 DRUG INTERACTIONS**

215 **7.1 Inhibitors of Cytochrome P450 3A4**

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

223 **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

224 Vilanterol, like other beta₂-agonists, should be administered with extreme caution to patients
225 being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to
226 prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the effect
227 of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs
228 that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

229 **7.3 Beta-adrenergic Receptor Blocking Agents**

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

236 **7.4 Non-Potassium-Sparing Diuretics**

237 The electrocardiographic changes and/or hypokalemia that may result from the administration of
238 non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by
239 beta-agonists, such as vilanterol, a component of ANORO ELLIPTA, especially when the
240 recommended dose of the beta-agonist is exceeded. Although the clinical significance of these
241 effects is not known, caution is advised in the coadministration of ANORO ELLIPTA with
242 non-potassium-sparing diuretics.

243 **7.5 Anticholinergics**

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

248 **8 USE IN SPECIFIC POPULATIONS**

249 **8.1 Pregnancy**

250 Risk Summary

251 There are insufficient data on the use of ANORO ELLIPTA or its individual components,
252 umeclidinium and vilanterol, in pregnant women to inform a drug-associated risk. (*See Clinical*
253 *Considerations.*) In animal reproduction studies, umeclidinium administered via inhalation or
254 subcutaneously to pregnant rats and rabbits was not associated with adverse effects on
255 embryofetal development at exposures approximately 50 and 200 times, respectively, the human
256 exposure at the maximum recommended human daily inhaled dose (MRHDID). Vilanterol
257 administered via inhalation to pregnant rats and rabbits produced no fetal structural abnormalities
258 at exposures approximately 70 times the MRHDID. (*See Data.*)

259 The estimated risk of major birth defects and miscarriage for the indicated populations is
260 unknown. In the U.S. general population, the estimated risk of major birth defects and
261 miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

262 Clinical Considerations

263 *Labor and Delivery:* There are no human studies evaluating the effects of ANORO ELLIPTA,
264 umeclidinium, or vilanterol during labor and delivery. Because of the potential for beta-agonist
265 interference with uterine contractility, use of ANORO ELLIPTA during labor should be
266 restricted to those patients in whom the benefits clearly outweigh the risks.

267 Data

268 *Animal Data:* The combination of umeclidinium and vilanterol has not been studied in pregnant
269 animals. Studies in pregnant animals have been conducted with umeclidinium and vilanterol
270 individually.

271 *Umeclidinium:* In separate embryofetal developmental studies, pregnant rats and rabbits
272 received umeclidinium during the period of organogenesis at doses up to approximately 50 and
273 200 times the MRHDID, respectively (on an AUC basis at maternal inhalation doses up to
274 278 mcg/kg/day in rats and at maternal subcutaneous doses up to 180 mcg/kg/day in rabbits). No
275 evidence of teratogenic effects was observed in either species.

276 In a perinatal and postnatal developmental study in rats, dams received umeclidinium during late
277 gestation and lactation periods with no evidence of effects on offspring development at doses up
278 to approximately 26 times the MRHDID (on an AUC basis at maternal subcutaneous doses up to
279 60 mcg/kg/day).

280 *Vilanterol:* In separate embryofetal developmental studies, pregnant rats and rabbits
281 received vilanterol during the period of organogenesis at doses up to approximately 13,000 and
282 450 times, respectively, the MRHDID (on a mcg/m² basis at maternal inhalation doses up to
283 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to
284 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose
285 in rats or in rabbits up to approximately 70 times the MRHDID (on an AUC basis at maternal
286 doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in
287 rabbits at approximately 450 times the MRHDID (on an AUC basis at maternal inhaled or
288 subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included
289 decreased or absent ossification in cervical vertebral centrum and metacarpals.

290 In a perinatal and postnatal developmental study in rats, dams received vilanterol during late
291 gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a
292 mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in
293 offspring development was observed.

294 **8.2 Lactation**

295 Risk Summary

296 There is no information available on the presence of umeclidinium or vilanterol in human milk,
297 the effects on the breastfed child, or the effects on milk production. Umeclidinium was detected
298 in the plasma of offspring of lactating rats treated with umeclidinium suggesting its presence in
299 maternal milk. (*See Data.*) The developmental and health benefits of breastfeeding should be
300 considered along with the mother's clinical need for ANORO ELLIPTA and any potential
301 adverse effects on the breastfed child from umeclidinium or vilanterol or from the underlying
302 maternal condition.

303 Data

304 Subcutaneous administration of umeclidinium to lactating rats at ≥ 60 mcg/kg/day resulted in a
305 quantifiable level of umeclidinium in 2 of 54 pups, which may indicate transfer of umeclidinium
306 in milk.

307 **8.4 Pediatric Use**

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

310 **8.5 Geriatric Use**

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

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

317 **8.6 Hepatic Impairment**

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

322 **8.7 Renal Impairment**

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

326 **10 OVERDOSAGE**

327 No case of overdose has been reported with ANORO ELLIPTA.

328 ANORO ELLIPTA contains both umeclidinium and vilanterol; therefore, the risks associated
329 with overdosage for the individual components described below apply to ANORO ELLIPTA.
330 Treatment of overdosage consists of discontinuation of ANORO ELLIPTA together with
331 institution of appropriate symptomatic and/or supportive therapy. The judicious use of a
332 cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can
333 produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

334 10.1 Umeclidinium

335 High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there
336 were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to
337 1,000 mcg of umeclidinium (16 times the maximum recommended daily dose) for 14 days in
338 subjects with COPD.

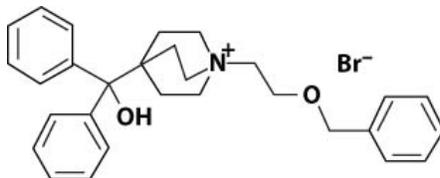
339 10.2 Vilanterol

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

347 11 DESCRIPTION

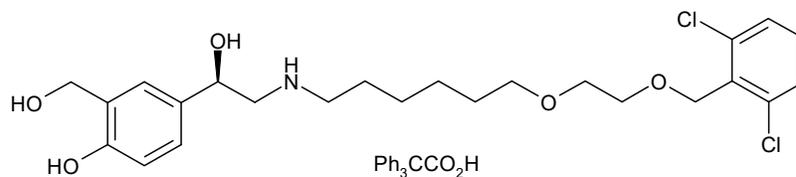
348 ANORO ELLIPTA is an inhalation powder drug product for delivery of a combination of
349 umeclidinium (an anticholinergic) and vilanterol (a LABA) to patients by oral inhalation.

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



353
354 Umeclidinium bromide is a white powder with a molecular weight of 508.5, and the empirical
355 formula is $C_{29}H_{34}NO_2 \cdot Br$ (as a quaternary ammonium bromide compound). It is slightly soluble
356 in water.

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



360

361 Vilanterol trifenate is a white powder with a molecular weight of 774.8, and the empirical
362 formula is C₂₄H₃₃Cl₂NO₅•C₂₀H₁₆O₂. It is practically insoluble in water.

363 ANORO ELLIPTA is a light grey and red plastic inhaler containing 2 foil blister strips. Each
364 blister on one strip contains a white powder mix of micronized umeclidinium bromide (74.2 mcg
365 equivalent to 62.5 mcg of umeclidinium), magnesium stearate (75 mcg), and lactose
366 monohydrate (to 12.5 mg), and each blister on the other strip contains a white powder mix of
367 micronized vilanterol trifenate (40 mcg equivalent to 25 mcg of vilanterol), magnesium
368 stearate (125 mcg), and lactose monohydrate (to 12.5 mg). The lactose monohydrate contains
369 milk proteins. After the inhaler is activated, the powder within both blisters is exposed and ready
370 for dispersion into the airstream created by the patient inhaling through the mouthpiece.

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

373 In adult subjects with obstructive lung disease and severely compromised lung function (COPD
374 with FEV₁/FVC <70% and FEV₁ <30% predicted or FEV₁ <50% predicted plus chronic
375 respiratory failure), mean peak inspiratory flow through the ELLIPTA inhaler was 66.5 L/min
376 (range: 43.5 to 81.0 L/min).

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

379 12 CLINICAL PHARMACOLOGY

380 12.1 Mechanism of Action

381 ANORO ELLIPTA

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

386 Umeclidinium

387 Umeclidinium is a long-acting muscarinic antagonist, which is often referred to as an
388 anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the
389 airways, it exhibits pharmacological effects through inhibition of M3 receptors at the smooth
390 muscle leading to bronchodilation. The competitive and reversible nature of antagonism was
391 shown with human and animal origin receptors and isolated organ preparations. In preclinical in

392 vitro as well as in vivo studies, prevention of methacholine- and acetylcholine-induced
393 bronchoconstrictive effects was dose-dependent and lasted longer than 24 hours. The clinical
394 relevance of these findings is unknown. The bronchodilation following inhalation of
395 umeclidinium is predominantly a site-specific effect.

396 Vilanterol

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

399 Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle
400 and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in
401 the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise
402 function of these receptors has not been established, but they raise the possibility that even
403 highly selective beta₂-agonists may have cardiac effects.

404 The pharmacologic effects of beta₂-adrenergic agonist drugs, including vilanterol, are at least in
405 part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the
406 conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic
407 AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition
408 of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

409 **12.2 Pharmacodynamics**

410 Cardiovascular Effects

411 *Healthy Subjects:* QTc interval prolongation was studied in a double-blind, multiple-dose,
412 placebo- and positive-controlled crossover trial in 86 healthy subjects. The maximum mean
413 (95% upper confidence bound) difference in QTcF from placebo after baseline correction was
414 4.6 (7.1) milliseconds and 8.2 (10.7) milliseconds for umeclidinium/vilanterol 125 mcg/25 mcg
415 and umeclidinium/vilanterol 500 mcg/100 mcg (8/4 times the recommended dosage),
416 respectively.

417 A dose-dependent increase in heart rate was also observed. The maximum mean (95% upper
418 confidence bound) difference in heart rate from placebo after baseline correction was
419 8.8 (10.5) beats/min and 20.5 (22.3) beats/min seen 10 minutes after dosing for
420 umeclidinium/vilanterol 125 mcg/25 mcg and umeclidinium/vilanterol 500 mcg/100 mcg,
421 respectively.

422 *Chronic Obstructive Pulmonary Disease:* The effect of ANORO ELLIPTA on cardiac rhythm in
423 subjects diagnosed with COPD was assessed using 24-hour Holter monitoring in 6- and
424 12-month trials: 53 subjects received ANORO ELLIPTA, 281 subjects received
425 umeclidinium/vilanterol 125 mcg/25 mcg, and 182 subjects received placebo. No clinically
426 meaningful effects on cardiac rhythm were observed.

427 **12.3 Pharmacokinetics**

428 Linear pharmacokinetics was observed for umeclidinium (62.5 to 500 mcg) and vilanterol (25 to
429 100 mcg).

430 Absorption

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

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

441 Distribution

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

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

447 Metabolism

448 *Umeclidinium:* In vitro data showed that umeclidinium is primarily metabolized by the enzyme
449 cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter.
450 The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation)
451 followed by conjugation (e.g., glucuronidation), resulting in a range of metabolites with either
452 reduced pharmacological activity or for which the pharmacological activity has not been
453 established. Systemic exposure to the metabolites is low.

454 *Vilanterol:* In vitro data showed that vilanterol is metabolized principally by CYP3A4 and is a
455 substrate for the P-gp transporter. Vilanterol is metabolized to a range of metabolites with
456 significantly reduced β_1 - and β_2 -agonist activity.

457 Elimination

458 *Umeclidinium:* The effective half-life after once-daily inhaled dosing is 11 hours. Following
459 intravenous dosing with radiolabeled umeclidinium, mass balance showed 58% of the radiolabel
460 in the feces and 22% in the urine. The excretion of the drug-related material in the feces
461 following intravenous dosing indicated elimination in the bile. Following oral dosing to healthy

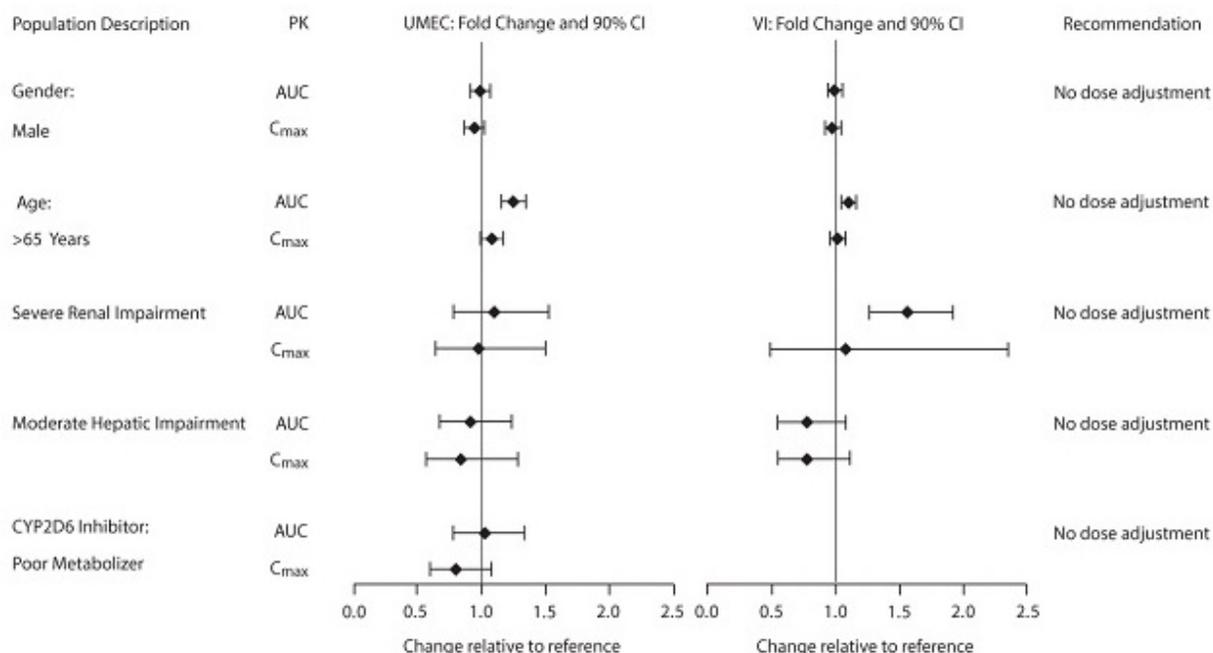
462 male subjects, radiolabel recovered in feces was 92% of the total dose and that in urine was <1%
 463 of the total dose, suggesting negligible oral absorption.

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

467 Specific Populations

468 The effects of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics
 469 of umeclidinium and vilanterol are shown in Figure 1. Population pharmacokinetic analysis
 470 showed no evidence of a clinically significant effect of age (40 to 93 years) (Figure 1), gender
 471 (69% male) (Figure 1), inhaled corticosteroid use (48%), or weight (34 to 161 kg) on systemic
 472 exposure of either umeclidinium or vilanterol. In addition, there was no evidence of a clinically
 473 significant effect of race.

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



476
 477 *Patients with Hepatic Impairment*: The impact of hepatic impairment on the pharmacokinetics of
 478 ANORO ELLIPTA has been evaluated in subjects with moderate hepatic impairment
 479 (Child-Pugh score of 7-9). There was no evidence of an increase in systemic exposure to either
 480 umeclidinium or vilanterol (C_{max} and AUC) (Figure 1). There was no evidence of altered protein
 481 binding in subjects with moderate hepatic impairment compared with healthy subjects. ANORO
 482 ELLIPTA has not been evaluated in subjects with severe hepatic impairment.

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

489 Drug Interaction Studies

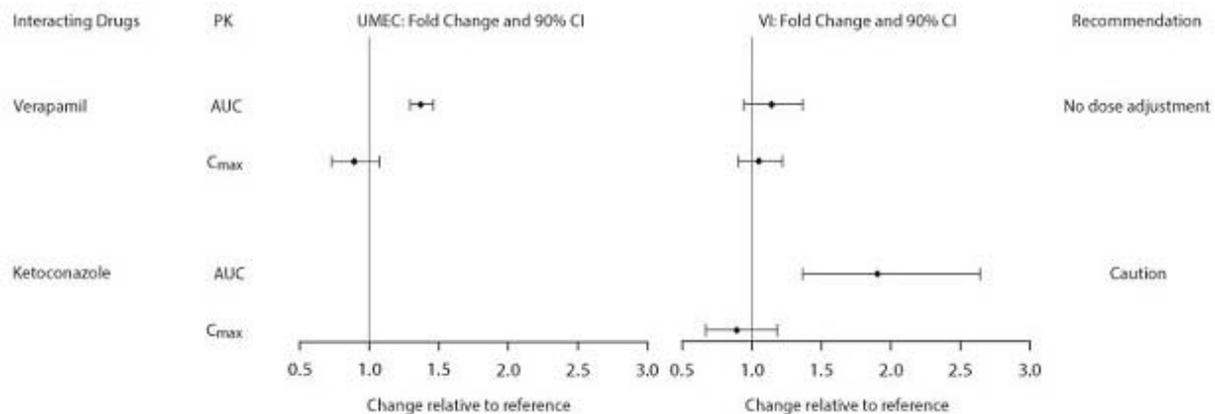
490 When umeclidinium and vilanterol were administered in combination by the inhaled route, the
491 pharmacokinetic parameters for each component were similar to those observed when each
492 active substance was administered separately.

493 *Inhibitors of Cytochrome P450 3A4:* Vilanterol is a substrate of CYP3A4. A double-blind,
494 repeat-dose, 2-way crossover drug interaction trial was conducted in healthy subjects to
495 investigate the pharmacokinetic and pharmacodynamic effects of vilanterol 25 mcg as an
496 inhalation powder with ketoconazole 400 mg. The plasma concentrations of vilanterol were
497 higher after single and repeated doses when coadministered with ketoconazole than with placebo
498 (Figure 2). The increase in vilanterol exposure was not associated with an increase in
499 beta-agonist-related systemic effects on heart rate or blood potassium.

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

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

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



512

513 **13 NONCLINICAL TOXICOLOGY**

514 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

515 ANORO ELLIPTA

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

519 Umeclidinium

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

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

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

529 Vilanterol

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

535 In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in
536 mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhalation
537 doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 20 times
538 the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of
539 10.5 mcg/kg/day (approximately equivalent to the MRHDID in adults on an AUC basis).

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

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

546 No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol
547 doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the
548 MRHDID based on AUC).

549 **14 CLINICAL STUDIES**

550 The safety and efficacy of ANORO ELLIPTA were evaluated in a clinical development program
551 that included 6 dose-ranging trials, 4 lung function trials of 6 months' duration (2 placebo
552 controlled and 2 active controlled), two 12-week crossover trials, and a 12-month long-term
553 safety trial. The efficacy of ANORO ELLIPTA is based primarily on the dose-ranging trials in
554 1,908 subjects with COPD or asthma [*see Clinical Studies (14.1)*] and the 2 placebo-controlled
555 confirmatory trials, with additional support from the 2 active-controlled and 2 crossover trials in
556 5,388 subjects with COPD, including chronic bronchitis and/or emphysema [*see Clinical Studies*
557 *(14.2)*]. Evidence of efficacy for ANORO ELLIPTA on COPD exacerbations was established by
558 the efficacy of the umeclidinium component as part of a fixed-dose combination with an
559 ICS/LABA, as assessed in a 12-month trial in 10,355 subjects [*see Clinical Studies (14.2)*].

560 **14.1 Dose-Ranging Trials**

561 Dose selection for ANORO ELLIPTA in COPD was based on dose-ranging trials for the
562 individual components, vilanterol and umeclidinium. Based on the findings from these studies,
563 once-daily doses of umeclidinium/vilanterol 62.5 mcg/25 mcg and umeclidinium/vilanterol
564 125 mcg/25 mcg were evaluated in the confirmatory COPD trials. **ANORO ELLIPTA is not**
565 **indicated for asthma.**

566 Umeclidinium

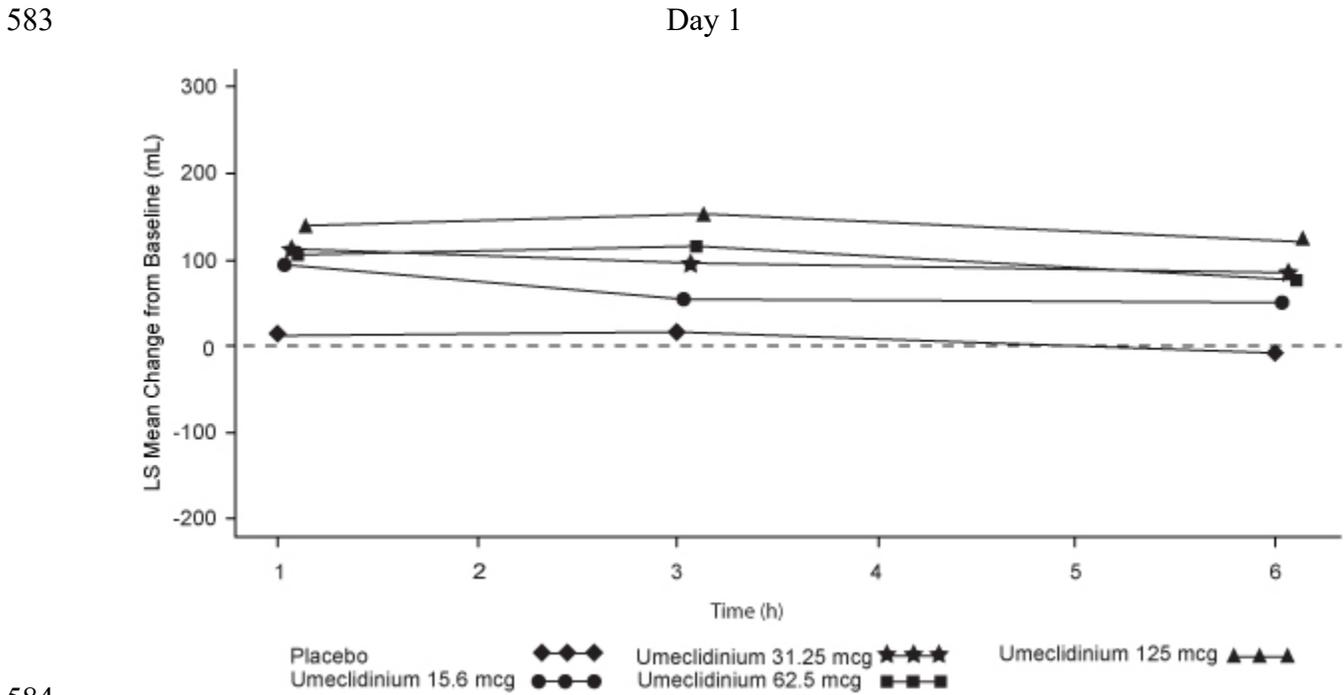
567 Dose selection for umeclidinium in COPD was supported by a 7-day, randomized, double-blind,
568 placebo-controlled, crossover trial evaluating 4 doses of umeclidinium (15.6 to 125 mcg) or
569 placebo dosed once daily in the morning in 163 subjects with COPD. A dose ordering was

570 observed, with the 62.5- and 125-mcg doses demonstrating larger improvements in FEV₁ over
571 24 hours compared with the lower doses of 15.6 and 31.25 mcg (Figure 3).

572 The differences in trough FEV₁ from baseline after 7 days for placebo and the 15.6-, 31.25-,
573 62.5-, and 125-mcg doses were -74 mL (95% CI: -118, -31), 38 mL (95% CI: -6, 83), 27 mL
574 (95% CI: -18, 72), 49 mL (95% CI: 6, 93), and 109 mL (95% CI: 65, 152), respectively. Two
575 additional dose-ranging trials in subjects with COPD demonstrated minimal additional benefit at
576 doses above 125 mcg. The dose-ranging results supported the evaluation of 2 doses of
577 umeclidinium, 62.5 and 125 mcg, in the confirmatory COPD trials to further assess dose
578 response.

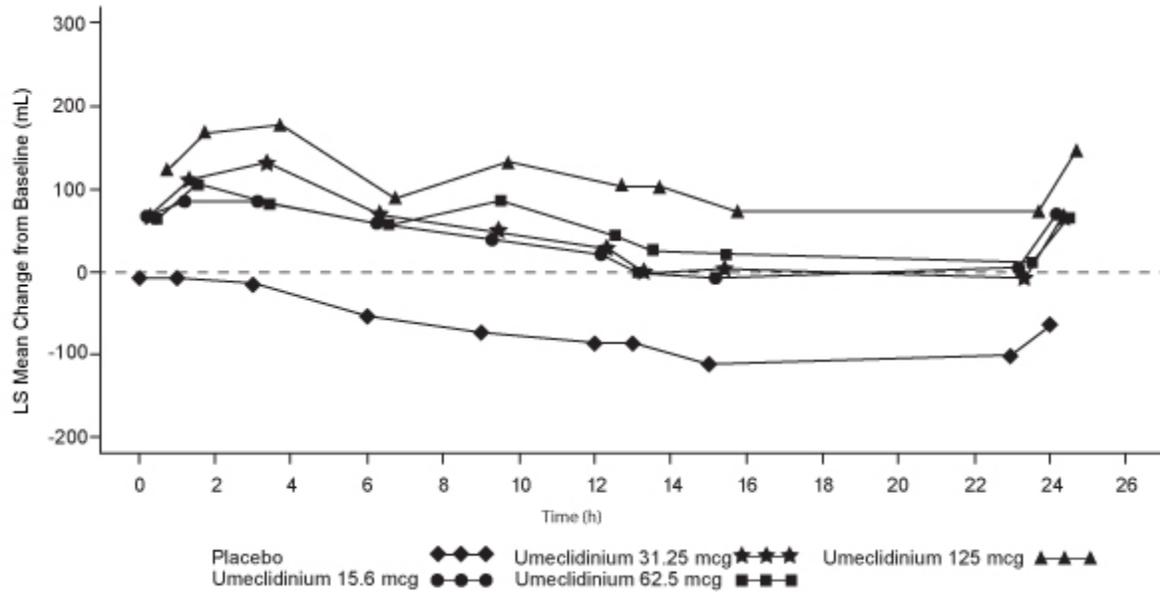
579 Evaluations of dosing interval by comparing once- and twice-daily dosing supported selection of
580 a once-daily dosing interval for further evaluation in the confirmatory COPD trials.

581 **Figure 3. Least Squares (LS) Mean Change from Baseline in Postdose Serial FEV₁ (mL)**
582 **on Days 1 and 7**



585

Day 7



586

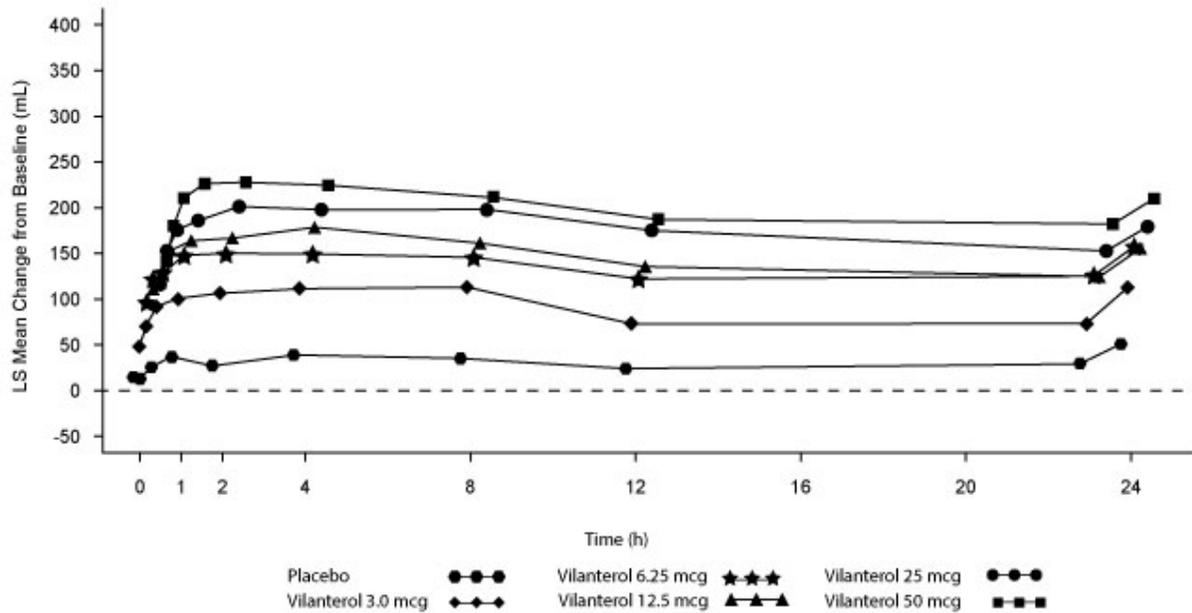
587 Vilanterol

588 Dose selection for vilanterol in COPD was supported by a 28-day, randomized, double-blind,
 589 placebo-controlled, parallel-group trial evaluating 5 doses of vilanterol (3 to 50 mcg) or placebo
 590 dosed in the morning in 602 subjects with COPD. Results demonstrated dose-related increases
 591 from baseline in FEV₁ at Day 1 and Day 28 (Figure 4).

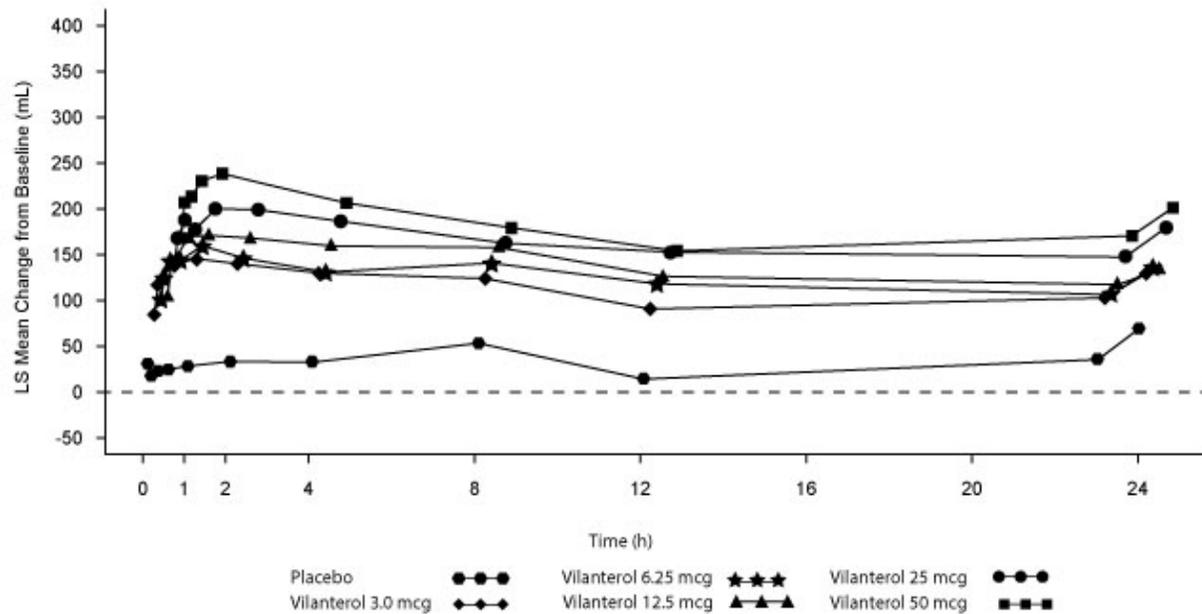
592 **Figure 4. Least Squares (LS) Mean Change from Baseline in Postdose Serial FEV₁**
 593 **(0-24 h) (mL) on Days 1 and 28**

594

Day 1



595



597

598 The differences in trough FEV₁ after Day 28 from baseline for placebo and the 3-, 6.25-, 12.5-,
 599 25-, and 50-mcg doses were 29 mL (95% CI: -8, 66), 120 mL (95% CI: 83, 158), 127 mL (95%
 600 CI: 90, 164), 138 mL (95% CI: 101, 176), 166 mL (95% CI: 129, 203), and 194 mL (95% CI:
 601 156, 231), respectively. These results supported the evaluation of vilanterol 25 mcg in the
 602 confirmatory trials for COPD.

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

606 14.2 Confirmatory Trials

607 Lung Function

608 The clinical development program for ANORO ELLIPTA included two 6-month, randomized,
 609 double-blind, placebo-controlled, parallel-group trials; two 6-month active-controlled trials; and
 610 two 12-week crossover trials in subjects with COPD designed to evaluate the efficacy of
 611 ANORO ELLIPTA on lung function. The 6-month trials treated 4,733 subjects that had a clinical
 612 diagnosis of COPD, were 40 years of age or older, had a history of smoking ≥ 10 pack-years, had
 613 a post-albuterol FEV₁ $\leq 70\%$ of predicted normal values, had a ratio of FEV₁/FVC of < 0.7 , and
 614 had a Modified Medical Research Council (mMRC) score ≥ 2 . Of the 4,713 subjects included in
 615 the efficacy analysis, 68% were male and 84% were white. They had a mean age of 63 years and
 616 an average smoking history of 45 pack-years, with 50% identified as current smokers. At
 617 screening, the mean postbronchodilator percent predicted FEV₁ was 48% (range: 13% to 76%),
 618 the mean postbronchodilator FEV₁/FVC ratio was 0.47 (range: 0.13 to 0.78), and the mean
 619 percent reversibility was 14% (range: -36% to 109%).

620 Trial 1 (NCT #01313650) evaluated ANORO ELLIPTA (umeclidinium/vilanterol
 621 62.5 mcg/25 mcg), umeclidinium 62.5 mcg, vilanterol 25 mcg, and placebo. The primary
 622 endpoint was change from baseline in trough (predose) FEV₁ at Day 169 (defined as the mean of
 623 the FEV₁ values obtained at 23 and 24 hours after the previous dose on Day 168) compared with
 624 placebo, umeclidinium 62.5 mcg, and vilanterol 25 mcg. The comparison of ANORO ELLIPTA
 625 with umeclidinium 62.5 mcg and vilanterol 25 mcg was assessed to evaluate the contribution of
 626 the individual comparators to ANORO ELLIPTA. ANORO ELLIPTA demonstrated a larger
 627 increase in mean change from baseline in trough (predose) FEV₁ relative to placebo,
 628 umeclidinium 62.5 mcg, and vilanterol 25 mcg (Table 2).

629 **Table 2. Least Squares Mean Change from Baseline in Trough FEV₁ (mL) at Day 169**
 630 **in the Intent-to-Treat Population (Trial 1)**

Treatment	n	Trough FEV ₁ (mL) at Day 169		
		Difference from		
		Placebo (95% CI) n = 280	Umeclidinium 62.5 mcg ^a (95% CI) n = 418	Vilanterol 25 mcg ^a (95% CI) n = 421
ANORO ELLIPTA	413	167 (128, 207)	52 (17, 87)	95 (60, 130)

631 n = Number in intent-to-treat population.

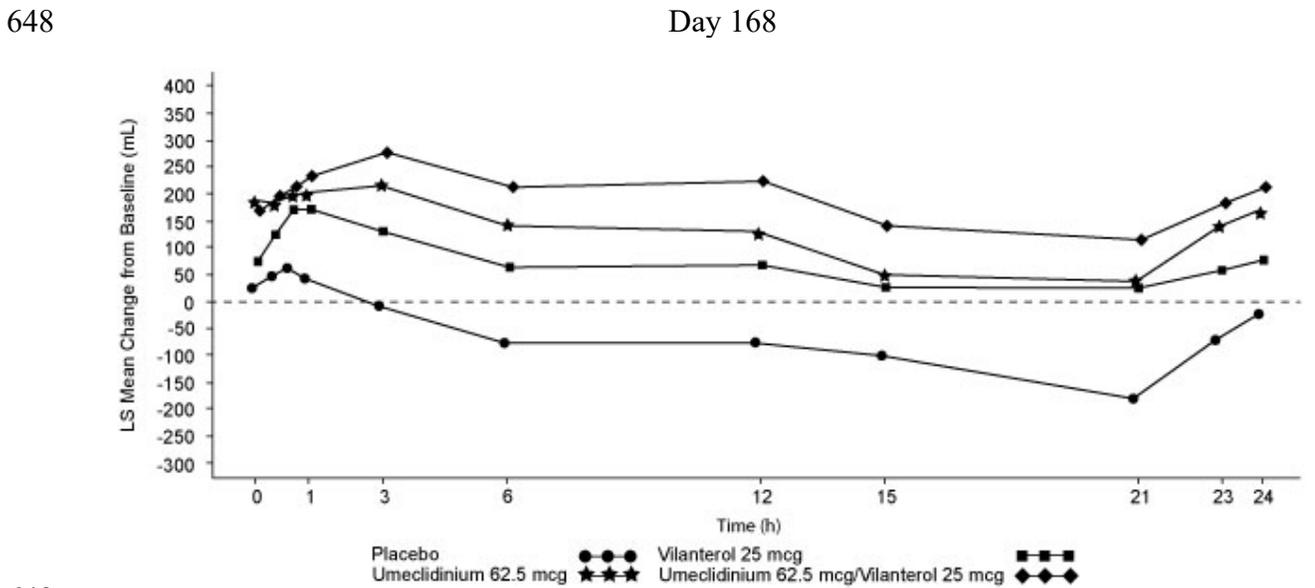
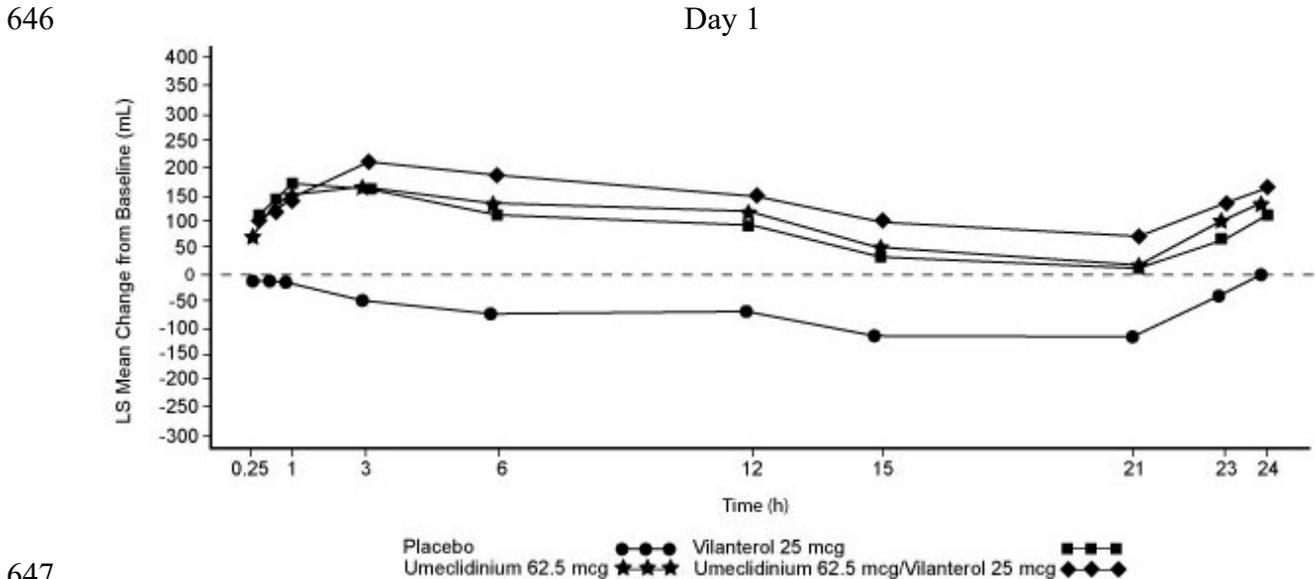
632 ^a The umeclidinium and vilanterol comparators used the same inhaler and excipients as
 633 ANORO ELLIPTA.

634 Trial 2 (NCT #01313637) had a similar study design as Trial 1 but evaluated
 635 umeclidinium/vilanterol 125 mcg/25 mcg, umeclidinium 125 mcg, vilanterol 25 mcg, and
 636 placebo. Results for umeclidinium/vilanterol 125 mcg/25 mcg in Trial 2 were similar to those
 637 observed for ANORO ELLIPTA in Trial 1.

638 Results from the 2 active-controlled trials and the two 12-week trials provided additional support
 639 for the efficacy of ANORO ELLIPTA in terms of change from baseline in trough FEV₁
 640 compared with the single-ingredient comparators and placebo.

641 Serial spirometric evaluations throughout the 24-hour dosing interval were performed in a subset
 642 of subjects (n = 197) at Days 1, 84, and 168 in Trial 1. Results from Trial 1 at Day 1 and Day
 643 168 are shown in Figure 5.

644 **Figure 5. Least Squares (LS) Mean Change from Baseline in FEV₁ (mL) over Time**
 645 **(0-24 h) on Days 1 and 168 (Trial 1 Subset Population)**



650 The peak FEV₁ was defined as the maximum FEV₁ recorded within 6 hours after the dose of trial
 651 medicine on Days 1, 28, 84, and 168 (measurements recorded at 15 and 30 minutes and 1, 3, and
 652 6 hours). The mean peak FEV₁ improvement from baseline for ANORO ELLIPTA compared
 653 with placebo at Day 1 and at Day 168 was 167 and 224 mL, respectively. The median time to
 654 onset on Day 1, defined as a 100-mL increase from baseline in FEV₁, was 27 minutes in subjects
 655 receiving ANORO ELLIPTA.

656 Exacerbations

657 In Trial 6 (NCT #02164513), a total of 10,355 subjects with COPD with a history of 1 or more
658 moderate or severe exacerbations in the prior 12 months were randomized (1:2:2) to receive
659 ANORO ELLIPTA (n = 2,070), fluticasone furoate/umeclidinium/vilanterol
660 100 mcg/62.5 mcg/25 mcg (n = 4,145), or fluticasone furoate/vilanterol 100 mcg/25 mcg
661 (n = 4,133) administered once daily in a 12-month trial. The population demographics across all
662 treatments were: mean age of 65 years, 77% white, 66% male, and an average smoking history
663 of 46.6 pack-years, with 35% identified as current smokers. At trial entry, the most common
664 COPD medications were ICS + anticholinergic + LABA (34%), ICS + LABA (26%),
665 anticholinergic + LABA (8%), and anticholinergic (7%). The mean postbronchodilator percent
666 predicted FEV₁ was 46% (standard deviation: 15%), the mean postbronchodilator FEV₁/FVC
667 ratio was 0.47 (standard deviation: 0.12), and the mean percent reversibility was 10% (range:
668 -59% to 125%).

669 The primary endpoint was annual rate of on-treatment moderate and severe exacerbations in
670 subjects treated with fluticasone furoate/umeclidinium/vilanterol compared with the fixed-dose
671 combinations of fluticasone furoate/vilanterol and ANORO ELLIPTA. Exacerbations were
672 defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum
673 purulence) or worsening of any 1 major symptom together with any 1 of the following minor
674 symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other
675 cause, and increased cough or wheeze for at least 2 consecutive days. Exacerbations were
676 considered to be of moderate severity if treatment with systemic corticosteroids and/or
677 antibiotics was required and were considered to be severe if resulted in hospitalization or death.

678 *Contribution of Umeclidinium on COPD Exacerbations:* Evidence of efficacy for ANORO
679 ELLIPTA on COPD exacerbations was established by the efficacy of the umeclidinium
680 component of fluticasone furoate/umeclidinium/vilanterol in Trial 6. Treatment with fluticasone
681 furoate/umeclidinium/vilanterol statistically significantly reduced the on-treatment annual rate of
682 moderate/severe exacerbations by 15% compared with fluticasone furoate/vilanterol (Table 3). A
683 reduction in risk of on-treatment moderate/severe exacerbation (as measured by time to first) was
684 also observed for the same comparison. The benefit of umeclidinium on exacerbations is not
685 expected to diminish when combined with vilanterol in ANORO ELLIPTA.

686 *ANORO ELLIPTA and COPD Exacerbations:* In Trial 6, the primary efficacy analysis of the rate
687 of moderate/severe exacerbations, treatment with fluticasone furoate/umeclidinium/vilanterol
688 statistically significantly reduced the on-treatment annual rate of moderate/severe exacerbations
689 by 25% compared with ANORO ELLIPTA (Table 3).

690 **Table 3. Moderate and Severe Chronic Obstructive Pulmonary Disease Exacerbations**
 691 **(Trial 6)^a**

Treatment	n	Mean Annual Rate (exacerbations/year)	FF/UMEC/VI Rate Ratio vs. Comparator (95% CI)	% Reduction in Exacerbation Rate (95% CI)	P Value
FF/UMEC/VI	4,145	0.91			
FF/VI	4,133	1.07	0.85 (0.80, 0.90)	15 (10, 20)	<i>P</i> <0.001
ANORO ELLIPTA	2,069	1.21	0.75 (0.70, 0.81)	25 (19, 30)	<i>P</i> <0.001

692 FF/UMEC/VI = Fluticasone furoate/umeclidinium/vilanterol 100 mcg/62.5 mcg/25 mcg,
 693 FF/VI = Fluticasone furoate/vilanterol 100 mcg/25 mcg, ANORO ELLIPTA =
 694 Umeclidinium/vilanterol 62.5 mcg/25 mcg.

695 ^a On-treatment analyses excluded exacerbation data collected after discontinuation of study
 696 treatment.

697 **16 HOW SUPPLIED/STORAGE AND HANDLING**

698 ANORO ELLIPTA is supplied as a disposable light grey and red plastic inhaler containing 2 foil
 699 strips, each with 30 blisters (or 7 blisters for the institutional pack). One strip contains
 700 umeclidinium (62.5 mcg per blister), and the other strip contains vilanterol (25 mcg per blister).
 701 A blister from each strip is used to create 1 dose. The inhaler is packaged in a
 702 moisture-protective foil tray with a desiccant and a peelable lid in the following packs:

703 NDC 0173-0869-10 30 inhalations (60 blisters)

704 NDC 0173-0869-06 7 inhalations (14 blisters), institutional pack

705 Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from
 706 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place
 707 away from direct heat or sunlight. Keep out of reach of children.

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

712 **17 PATIENT COUNSELING INFORMATION**

713 Advise the patient to read the FDA-approved patient labeling (Patient Information and
 714 Instructions for Use).

715 Serious Asthma-Related Events

716 ANORO ELLIPTA is not indicated for the treatment of asthma. Inform patients that LABA, such
717 as vilanterol (one of the active ingredients in ANORO ELLIPTA), when used alone (without
718 ICS) for asthma increase the risk of asthma-related hospitalization or asthma-related death.

719 Not for Acute Symptoms

720 Inform patients that ANORO ELLIPTA is not meant to relieve acute symptoms of COPD and
721 extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an
722 inhaled, short-acting beta₂-agonist such as albuterol. Provide patients with such medicine and
723 instruct them in how it should be used.

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

- 725 • Decreasing effectiveness of inhaled, short-acting beta₂-agonists
- 726 • Need for more inhalations than usual of inhaled, short-acting beta₂-agonists
- 727 • Significant decrease in lung function as outlined by the physician

728 Tell patients they should not stop therapy with ANORO ELLIPTA without healthcare provider
729 guidance since symptoms may recur after discontinuation.

730 Do Not Use Additional Long-acting Beta₂-agonists

731 Instruct patients not to use other medicines containing a LABA. Patients should not use more
732 than the recommended once-daily dose of ANORO ELLIPTA.

733 Instruct patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis to
734 discontinue the regular use of these products and use them only for the symptomatic relief of
735 acute symptoms.

736 Paradoxical Bronchospasm

737 As with other inhaled medicines, ANORO ELLIPTA can cause paradoxical bronchospasm. If
738 paradoxical bronchospasm occurs, instruct patients to discontinue ANORO ELLIPTA and
739 contact their healthcare provider right away.

740 Risks Associated with Beta-agonist Therapy

741 Inform patients of adverse effects associated with beta₂-agonists, such as palpitations, chest pain,
742 rapid heart rate, tremor, or nervousness.

743 Worsening of Narrow-Angle Glaucoma

744 Instruct patients to be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye
745 pain or discomfort, blurred vision, visual halos or colored images in association with red eyes
746 from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare
747 provider immediately if any of these signs or symptoms develop.

748 Worsening of Urinary Retention

749 Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing
750 urine, painful urination). Instruct patients to consult a healthcare provider immediately if any of
751 these signs or symptoms develop.

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754 ANORO ELLIPTA was developed in collaboration with Innoviva.

755 **INNOVIVA**



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757 GlaxoSmithKline

758 Research Triangle Park, NC 27709

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PATIENT INFORMATION

ANORO ELLIPTA (a-NOR oh e-LIP-ta) (umeclidinium and vilanterol inhalation powder) for oral inhalation use

What is ANORO ELLIPTA?

- ANORO ELLIPTA combines 2 medicines in one inhaler, an anticholinergic medicine (umeclidinium) and a long-acting beta₂-adrenergic agonist (LABA) medicine (vilanterol).
 - Anticholinergic medicines such as umeclidinium and LABA medicines such as vilanterol 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 long term (chronic) to treat people with chronic obstructive pulmonary disease (COPD). COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both.
- ANORO ELLIPTA is used as 1 inhalation 1 time each day to improve symptoms of COPD for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).
- **ANORO ELLIPTA is not used to treat sudden symptoms of COPD.** Always have a rescue inhaler (an inhaled, short-acting bronchodilator) with you to treat sudden symptoms of COPD. 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.

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 the end of this Patient Information for a complete list of ingredients in ANORO ELLIPTA.
- have asthma.

Before using ANORO ELLIPTA, tell your healthcare provider about all of your medical 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 milk proteins.
- are pregnant or plan to become pregnant. It is not known if ANORO ELLIPTA may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicines, umeclidinium and vilanterol, in ANORO ELLIPTA pass into your breast 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, acclidinium)
- atropine
- antifungal or anti-HIV medicines

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 Patient Information.

- **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. Ask your healthcare provider or pharmacist if you have any questions.
- Use ANORO ELLIPTA exactly as prescribed. **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 per day. Take your next dose at your usual time. Do not take 2 doses at 1 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 breathing problems.** 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, or your rescue inhaler does not work as well to relieve your symptoms.

What are the possible side effects of ANORO ELLIPTA?

ANORO ELLIPTA can cause serious side effects, including:

- **serious problems in people with asthma.** People with asthma who take LABA medicines, such as vilanterol (one of the medicines in ANORO ELLIPTA), without also using a medicine called an inhaled corticosteroid, have an increased risk of serious problems from asthma, including death.
 - Call your healthcare provider if breathing problems worsen over time while using ANORO ELLIPTA. You may need a different treatment.
 - **Get emergency medical care if:**
 - your breathing problems worsen quickly.
 - you use your rescue inhaler medicine, but it does not relieve your breathing problems.
- **COPD symptoms that get worse over time.** If your COPD symptoms worsen over time, do not increase your dose of ANORO ELLIPTA; instead call your healthcare provider.

- **symptoms of using too much of a LABA medicine, including:**
 - chest pain
 - fast or irregular heartbeat
 - tremor
 - increased blood pressure
 - headache
 - nervousness
- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop using ANORO ELLIPTA and call your healthcare provider right away.
- **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 your face, mouth, and tongue
 - breathing problems
- **effects on heart.**
 - increased blood pressure
 - a fast or irregular heartbeat, awareness of heartbeat
 - chest pain
- **effects on 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
 - blurred vision
 - red eyes
 - nausea or vomiting
 - seeing halos or bright colors around lights

If you have these symptoms, call your healthcare provider 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
 - urinating frequently
 - painful urination
 - urination in a weak stream or drips

If you have these symptoms of urinary retention, stop taking ANORO ELLIPTA and call your healthcare provider 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
- common cold symptoms
- pain in your arms or legs
- chest pain
- sinus infection
- constipation
- muscle spasms
- lower respiratory infection
- diarrhea
- neck pain

These are not all the possible side effects of ANORO ELLIPTA. For more information, ask your healthcare provider or pharmacist.

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

How should I store ANORO ELLIPTA?

- Store ANORO ELLIPTA at room temperature between 68°F and 77°F (20°C and 25°C).
- Store ANORO ELLIPTA in a dry place away from heat and sunlight.
- Store ANORO ELLIPTA in the unopened tray and only open when ready for use.
- Safely throw away ANORO ELLIPTA in the trash 6 weeks after you open the 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 the safe and effective use of ANORO ELLIPTA.

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

This Patient Information leaflet 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 is written for health professionals.

What are the ingredients in ANORO ELLIPTA?

Active ingredients: umeclidinium, vilanterol

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



For more information about ANORO ELLIPTA, call 1-888-825-5249 or visit our website at www.ANORO.com.

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ANORO ELLIPTA was developed in collaboration with Innoviva.

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ANR:XPIL

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: June 2019

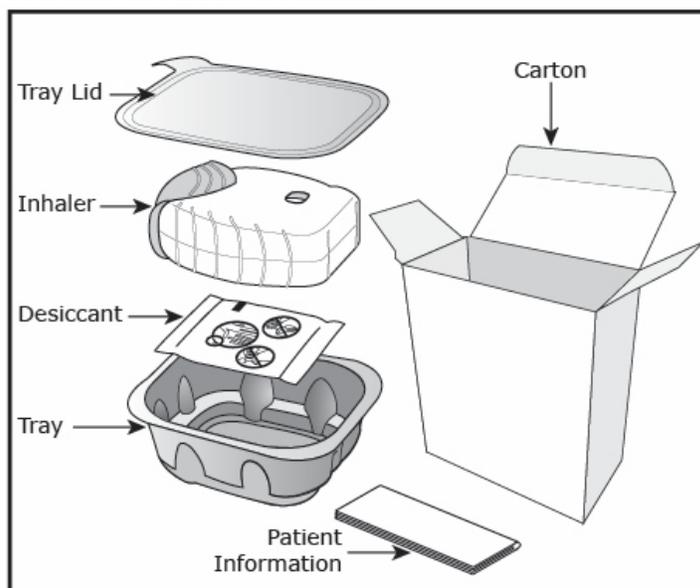
INSTRUCTIONS FOR USE

ANORO ELLIPTA (a-NOR oh e-LIP-ta) (umeclidinium and vilanterol inhalation powder) for oral inhalation use

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 1 inhalation.

Your ANORO ELLIPTA inhaler



How to use your inhaler

- ANORO ELLIPTA comes in a 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**.

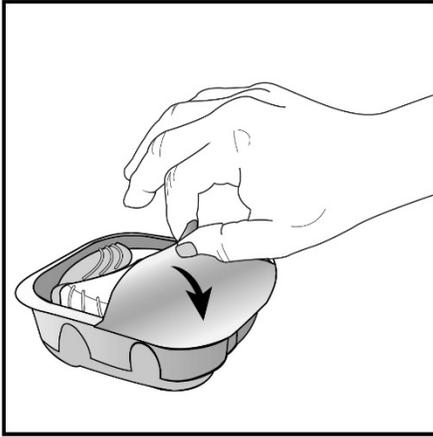


Figure A

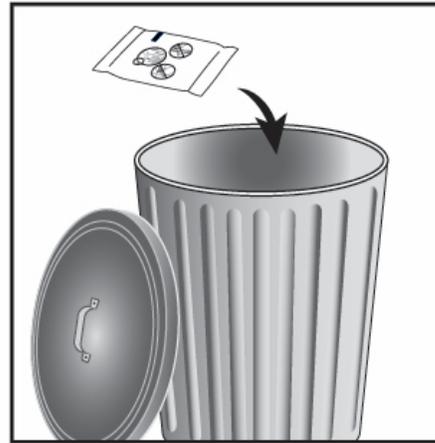


Figure B

Important Notes:

- Your inhaler contains 30 doses (7 doses if you have a sample or institutional pack).
- Each time you fully open the cover of the inhaler (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 1 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.

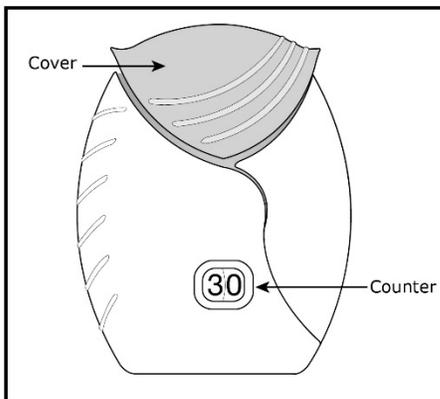


Figure C

- 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.

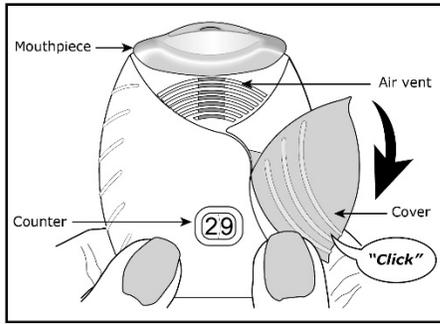


Figure D

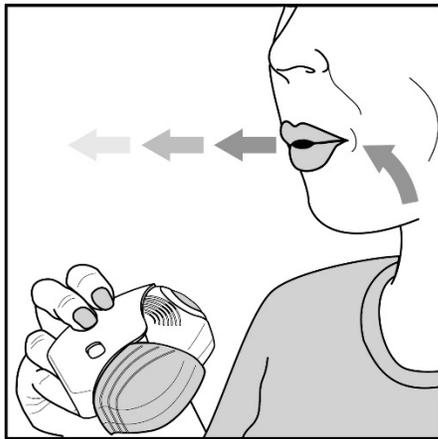


Figure E

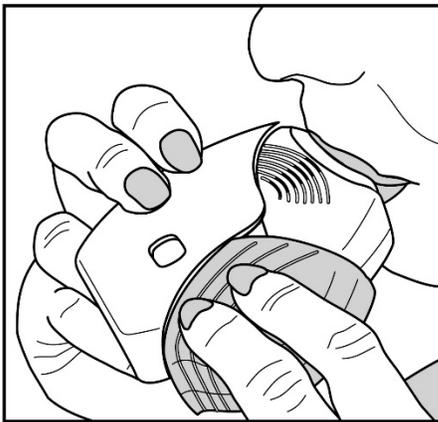


Figure F

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.

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.

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 1 long, steady, deep breath in through your mouth. **Do not** breathe in through your nose.

Do not block the air vent with your fingers.

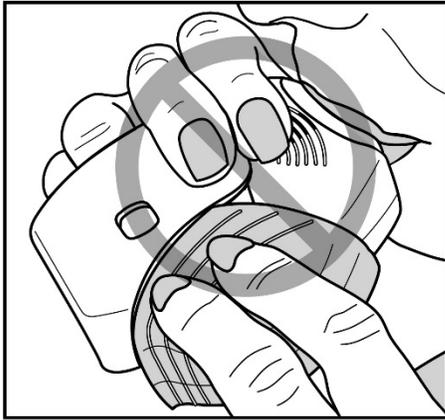


Figure G

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

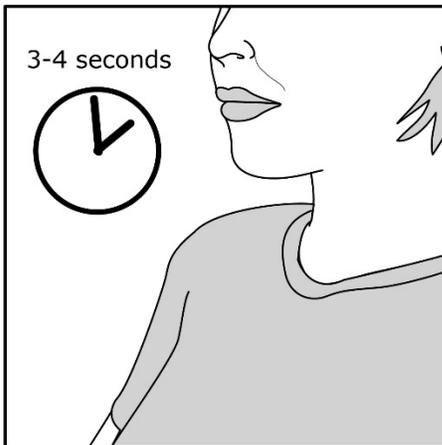


Figure H

- **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.**

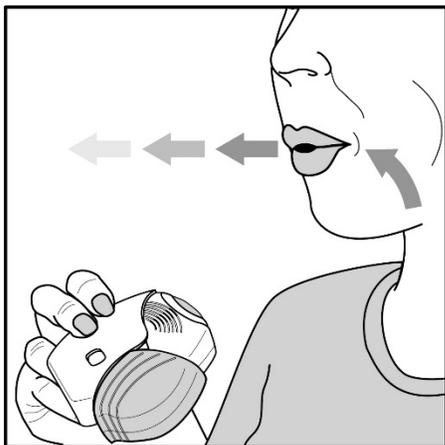


Figure I

- 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.

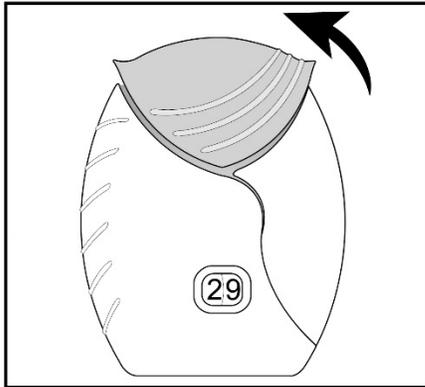


Figure J

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?

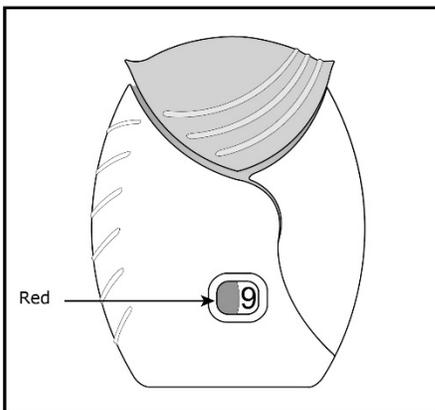


Figure K

- **When you have fewer 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.



For more information about ANORO ELLIPTA or how to use your inhaler, call 1-888-825-5249 or visit our website at www.ANORO.com.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BANU A KARIMI SHAH

06/06/2019 12:00:00 AM

signing with the delegated authority of Dr. Sally Seymour, Division Director, DPARP