

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**INCRUSE ELLIPTA (umeclidinium inhalation powder), for oral inhalation**

**Initial U.S. Approval: 2013**

----- **INDICATIONS AND USAGE** -----

INCRUSE ELLIPTA is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). (1)

----- **DOSAGE AND ADMINISTRATION** -----

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

----- **DOSAGE FORMS AND STRENGTHS** -----

Inhalation Powder. Inhaler containing a foil blister strip of powder formulation for oral inhalation. Each blister contains 62.5 mcg of umeclidinium. (3)

----- **CONTRAINDICATIONS** -----

- Severe hypersensitivity to milk proteins. (4)
- Hypersensitivity to any ingredient. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.1)

- If paradoxical bronchospasm occurs, discontinue INCRUSE ELLIPTA and institute alternative therapy. (5.2)
- 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. (5.4)
- 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. (5.5)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (incidence greater than or equal to 2% and more common than placebo) include nasopharyngitis, upper respiratory tract infection, cough, arthralgia. (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** -----

Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of INCRUSE ELLIPTA with other anticholinergic-containing drugs. (7.1)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**

**Revised: 10/2017**

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

<b>1</b>	<b>INDICATIONS AND USAGE</b>	
<b>2</b>	<b>DOSAGE AND ADMINISTRATION</b>	
<b>3</b>	<b>DOSAGE FORMS AND STRENGTHS</b>	
<b>4</b>	<b>CONTRAINDICATIONS</b>	
<b>5</b>	<b>WARNINGS AND PRECAUTIONS</b>	
5.1	Deterioration of Disease and Acute Episodes	
5.2	Paradoxical Bronchospasm	
5.3	Hypersensitivity Reactions	
5.4	Worsening of Narrow-angle Glaucoma	
5.5	Worsening of Urinary Retention	
<b>6</b>	<b>ADVERSE REACTIONS</b>	
6.1	Clinical Trials Experience	
6.2	Postmarketing Experience	
<b>7</b>	<b>DRUG INTERACTIONS</b>	
7.1	Anticholinergics	
<b>8</b>	<b>USE IN SPECIFIC POPULATIONS</b>	
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	
<b>10</b>	<b>OVERDOSAGE</b>	
<b>11</b>	<b>DESCRIPTION</b>	
<b>12</b>	<b>CLINICAL PHARMACOLOGY</b>	
12.1	Mechanism of Action	
12.2	Pharmacodynamics	
12.3	Pharmacokinetics	
<b>13</b>	<b>NONCLINICAL TOXICOLOGY</b>	
13.1	Carcinogenesis, Mutagenesis, Impairment of Fertility	
<b>14</b>	<b>CLINICAL STUDIES</b>	
14.1	Dose-Ranging Trials	
14.2	Maintenance Treatment: Confirmatory Trials	
14.3	Maintenance Treatment: Combination with an ICS/LABA Trials	
<b>16</b>	<b>HOW SUPPLIED/STORAGE AND HANDLING</b>	
<b>17</b>	<b>PATIENT COUNSELING INFORMATION</b>	

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

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**1 FULL PRESCRIBING INFORMATION**

**2 1 INDICATIONS AND USAGE**

3 INCRUSE ELLIPTA is indicated for the long-term, once-daily, maintenance treatment of  
4 airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including  
5 chronic bronchitis and/or emphysema.

**6 2 DOSAGE AND ADMINISTRATION**

7 INCRUSE ELLIPTA (umeclidinium 62.5 mcg) should be administered as 1 inhalation once  
8 daily by the orally inhaled route only.

9 INCRUSE ELLIPTA should be used at the same time every day. Do not use INCRUSE  
10 ELLIPTA more than 1 time every 24 hours.

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

### 13 **3 DOSAGE FORMS AND STRENGTHS**

14 Inhalation Powder. Disposable light grey and light green plastic inhaler containing a foil blister  
15 strip of powder intended for oral inhalation only. Each blister contains umeclidinium 62.5 mcg.

### 16 **4 CONTRAINDICATIONS**

17 The use of INCRUSE ELLIPTA is contraindicated in the following conditions:

- 18 • Severe hypersensitivity to milk proteins [*see Warnings and Precautions (5.3)*]
- 19 • Hypersensitivity to umeclidinium or any of the excipients [*see Warnings and Precautions*  
20 (*5.3*), *Description (11)*]

### 21 **5 WARNINGS AND PRECAUTIONS**

#### 22 **5.1 Deterioration of Disease and Acute Episodes**

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

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

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

#### 38 **5.2 Paradoxical Bronchospasm**

39 As with other inhaled medicines, INCRUSE ELLIPTA can produce paradoxical bronchospasm,  
40 which may be life threatening. If paradoxical bronchospasm occurs following dosing with  
41 INCRUSE ELLIPTA, it should be treated immediately with an inhaled, short-acting

42 bronchodilator; INCRUSE ELLIPTA should be discontinued immediately; and alternative  
43 therapy should be instituted.

### 44 **5.3 Hypersensitivity Reactions**

45 Hypersensitivity reactions such as anaphylaxis, angioedema, pruritus, rash, and urticaria may  
46 occur after administration of INCRUSE ELLIPTA. Discontinue INCRUSE ELLIPTA if such  
47 reactions occur. There have been reports of anaphylactic reactions in patients with severe milk  
48 protein allergy after inhalation of other powder products containing lactose; therefore, patients  
49 with severe milk protein allergy should not use INCRUSE ELLIPTA [*see Contraindications (4),*  
50 *Adverse Reactions (6.2)*].

### 51 **5.4 Worsening of Narrow-angle Glaucoma**

52 INCRUSE ELLIPTA should be used with caution in patients with narrow-angle glaucoma.  
53 Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma  
54 (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with  
55 red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a  
56 healthcare provider immediately if any of these signs or symptoms develops.

### 57 **5.5 Worsening of Urinary Retention**

58 INCRUSE ELLIPTA should be used with caution in patients with urinary retention. Prescribers  
59 and patients should be alert for signs and symptoms of urinary retention (e.g., difficulty passing  
60 urine, painful urination), especially in patients with prostatic hyperplasia or bladder-neck  
61 obstruction. Instruct patients to consult a healthcare provider immediately if any of these signs or  
62 symptoms develops.

## 63 **6 ADVERSE REACTIONS**

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

- 65 • Paradoxical bronchospasm [*see Warnings and Precautions (5.2)*]
- 66 • Worsening of narrow-angle glaucoma [*see Warnings and Precautions (5.4)*]
- 67 • Worsening of urinary retention [*see Warnings and Precautions (5.5)*]

### 68 **6.1 Clinical Trials Experience**

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

72 In the 8 clinical trials conducted to support initial approval of INCRUSE ELLIPTA, a total of  
73 1,663 subjects with COPD (mean age: 62.7 years; 89% white; 65% male across all treatments,  
74 including placebo) received at least 1 inhalation dose of umeclidinium at doses of 62.5 or  
75 125 mcg. In the 4 randomized, double-blind, placebo- or active-controlled, efficacy clinical

76 trials, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received  
 77 the recommended dose of umeclidinium 62.5 mcg. In a 12-month, randomized, double-blind,  
 78 placebo-controlled, long-term safety trial, 227 subjects received umeclidinium 125 mcg for up to  
 79 52 weeks [see *Clinical Studies (14)*].

80 The incidence of adverse reactions associated with INCRUSE ELLIPTA in Table 1 is based  
 81 upon 2 placebo-controlled efficacy trials: one 12-week trial and one 24-week trial.

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

<b>Adverse Reaction</b>	<b>INCRUSE ELLIPTA (n = 487) %</b>	<b>Placebo (n = 348) %</b>
Infections and infestations		
Nasopharyngitis	8%	7%
Upper respiratory tract infection	5%	4%
Pharyngitis	1%	<1%
Viral upper respiratory tract infection	1%	<1%
Respiratory, thoracic, and mediastinal disorders		
Cough	3%	2%
Musculoskeletal and connective tissue disorders		
Arthralgia	2%	1%
Myalgia	1%	<1%
Gastrointestinal disorders		
Abdominal pain upper	1%	<1%
Toothache	1%	<1%
Injury, poisoning, and procedural complications		
Contusion	1%	<1%
Cardiac disorders		
Tachycardia	1%	<1%

84 Other adverse reactions with INCRUSE ELLIPTA observed with an incidence less than 1% but  
 85 more common than placebo included atrial fibrillation.

86 In a long-term safety trial, 336 subjects (n = 227 umeclidinium 125 mcg, n = 109 placebo) were  
 87 treated for up to 52 weeks with umeclidinium 125 mcg or placebo. The demographic and  
 88 baseline characteristics of the long-term safety trial were similar to those of the efficacy trials  
 89 described above. Adverse reactions that occurred with a frequency greater than or equal to 1% in  
 90 subjects receiving umeclidinium 125 mcg that exceeded that in placebo in this trial were:  
 91 nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis, pneumonia,  
 92 lower respiratory tract infection, rhinitis, supraventricular tachycardia, supraventricular  
 93 extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache,

94 cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea,  
95 rash, depression, and vertigo.

96 The safety and efficacy of INCRUSE ELLIPTA in combination with an inhaled  
97 corticosteroid/long-acting beta<sub>2</sub>-adrenergic agonist (ICS/LABA) were also evaluated in four  
98 12-week clinical trials. A total of 1,637 subjects with COPD across four 12-week, randomized,  
99 double-blind clinical trials received at least 1 dose of INCRUSE ELLIPTA (62.5 mcg) or  
100 placebo administered once daily in addition to background ICS/LABA (mean age: 64 years, 88%  
101 white, 65% male across all treatments). Two trials (Trials 1 and 2) evaluated INCRUSE  
102 ELLIPTA in combination with fluticasone furoate/vilanterol (FF/VI) 100 mcg/25 mcg  
103 administered once daily, and 2 trials (Trials 3 and 4) evaluated INCRUSE ELLIPTA  
104 administered once daily in combination with fluticasone propionate/salmeterol (FP/SAL)  
105 250 mcg/50 mcg administered twice daily [*see Clinical Studies (14.2)*]. Adverse reactions that  
106 occurred with INCRUSE ELLIPTA in combination with an ICS/LABA were similar to those  
107 reported with INCRUSE ELLIPTA as monotherapy. In addition to the umeclidinium  
108 monotherapy adverse reactions reported above, adverse reactions occurring with INCRUSE  
109 ELLIPTA in combination with an ICS/LABA, at an incidence of greater than or equal to 1% and  
110 exceeding ICS/LABA alone, were oropharyngeal pain and dysgeusia.

## 111 **6.2 Postmarketing Experience**

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

### 118 Eye Disorders

119 Eye pain, glaucoma, vision blurred.

### 120 Immune System Disorders

121 Hypersensitivity reactions, including anaphylaxis, angioedema, pruritus, and urticaria.

### 122 Renal and Urinary Disorders

123 Dysuria, urinary retention.

## 124 **7 DRUG INTERACTIONS**

### 125 **7.1 Anticholinergics**

126 There is potential for an additive interaction with concomitantly used anticholinergic medicines.  
127 Therefore, avoid coadministration of INCRUSE ELLIPTA with other anticholinergic-containing

128 drugs as this may lead to an increase in anticholinergic adverse effects [*see Warnings and*  
129 *Precautions (5.4, 5.5), Adverse Reactions (6)*].

## 130 **8 USE IN SPECIFIC POPULATIONS**

### 131 **8.1 Pregnancy**

#### 132 Teratogenic Effects

133 Pregnancy Category C. There are no adequate and well-controlled trials with INCRUSE  
134 ELLIPTA in pregnant women. Because animal reproduction studies are not always predictive of  
135 human response, INCRUSE ELLIPTA should be used during pregnancy only if the potential  
136 benefit justifies the potential risk to the fetus. Women should be advised to contact their  
137 healthcare providers if they become pregnant while taking INCRUSE ELLIPTA.

138 There were no teratogenic effects in rats and rabbits at approximately 50 and 200 times,  
139 respectively, the maximum recommended human daily inhaled dose (MRHDID) in adults (on an  
140 AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and maternal subcutaneous  
141 doses up to 180 mcg/kg/day in rabbits).

#### 142 Nonteratogenic Effects

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

### 145 **8.2 Labor and Delivery**

146 There are no adequate and well-controlled human trials that have investigated the effects of  
147 INCRUSE ELLIPTA during labor and delivery. INCRUSE ELLIPTA should be used during  
148 labor only if the potential benefit justifies the potential risk.

### 149 **8.3 Nursing Mothers**

150 It is not known whether umeclidinium is excreted in human breast milk. Because many drugs are  
151 excreted in human milk, caution should be exercised when INCRUSE ELLIPTA is administered  
152 to a nursing woman. Since there are no data from well-controlled human studies on the use of  
153 INCRUSE ELLIPTA by nursing mothers, a decision should be made whether to discontinue  
154 nursing or to discontinue INCRUSE ELLIPTA, taking into account the importance of INCRUSE  
155 ELLIPTA to the mother.

156 Subcutaneous administration of umeclidinium to lactating rats at approximately 25 times the  
157 MRHDID in adults resulted in a quantifiable level of umeclidinium in 2 pups, which may  
158 indicate transfer of umeclidinium in milk.

### 159 **8.4 Pediatric Use**

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

162 **8.5 Geriatric Use**

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

165 Clinical trials of INCRUSE ELLIPTA included 810 subjects aged 65 years and older, and, of  
166 those, 183 subjects were aged 75 years and older. No overall differences in safety or  
167 effectiveness were observed between these subjects and younger subjects, and other reported  
168 clinical experience has not identified differences in responses between the elderly and younger  
169 subjects.

170 **8.6 Hepatic Impairment**

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

175 **8.7 Renal Impairment**

176 Patients with severe renal impairment (creatinine clearance less than 30 mL/min) showed no  
177 relevant increases in  $C_{max}$  or AUC, nor did protein binding differ between subjects with severe  
178 renal impairment and their healthy controls. No dosage adjustment is required in patients with  
179 renal impairment [*see Clinical Pharmacology (12.3)*].

180 **10 OVERDOSAGE**

181 No case of overdose has been reported with INCRUSE ELLIPTA.

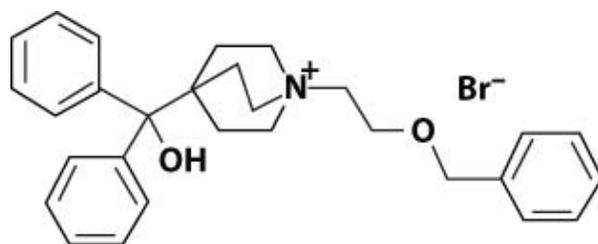
182 High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there  
183 were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to  
184 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in  
185 subjects with COPD.

186 Treatment of overdose consists of discontinuation of INCRUSE ELLIPTA together with  
187 institution of appropriate symptomatic and/or supportive therapy.

188 **11 DESCRIPTION**

189 INCRUSE ELLIPTA contains the active ingredient umeclidinium, an anticholinergic.

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



193  
194 Umeclidinium bromide is a white powder with a molecular weight of 508.5, and the empirical  
195 formula is  $C_{29}H_{34}NO_2 \cdot Br$  (as a quaternary ammonium bromide compound). It is slightly soluble  
196 in water.

197 INCRUSE ELLIPTA is a light grey and light green plastic inhaler containing a foil blister strip.  
198 Each blister on the strip contains a white powder mix of micronized umeclidinium bromide  
199 (74.2 mcg equivalent to 62.5 mcg of umeclidinium), magnesium stearate (75 mcg), and lactose  
200 monohydrate (to 12.5 mg). The lactose monohydrate contains milk proteins. After the inhaler is  
201 activated, the powder within the blister is exposed and ready for dispersion into the airstream  
202 created by the patient inhaling through the mouthpiece.

203 Under standardized *in vitro* test conditions, INCRUSE ELLIPTA delivers 55 mcg of  
204 umeclidinium per blister when tested at a flow rate of 60 L/min for 4 seconds.

205 In adult subjects with obstructive lung disease and severely compromised lung function (COPD  
206 with forced expiratory volume in 1 second/forced vital capacity [ $FEV_1/FVC$ ] less than 70% and  
207  $FEV_1$  less than 30% predicted or  $FEV_1$  less than 50% predicted plus chronic respiratory failure),  
208 mean peak inspiratory flow through the ELLIPTA inhaler was 67.5 L/min (range: 41.6 to  
209 83.3 L/min).

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

## 212 **12 CLINICAL PHARMACOLOGY**

### 213 **12.1 Mechanism of Action**

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

223 **12.2 Pharmacodynamics**

224 Cardiac Electrophysiology

225 QTc interval prolongation was studied in a double-blind, multiple dose, placebo- and  
226 positive-controlled, crossover trial in 86 healthy subjects. Following repeat doses of  
227 umeclidinium 500 mcg once daily (8 times the recommended dosage) for 10 days, umeclidinium  
228 does not prolong QTc to any clinically relevant extent.

229 **12.3 Pharmacokinetics**

230 Linear pharmacokinetics was observed for umeclidinium (62.5 to 500 mcg).

231 Absorption

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

237 Distribution

238 Following intravenous administration to healthy subjects, the mean volume of distribution was  
239 86 L. *In vitro* plasma protein binding in human plasma was on average 89%.

240 Metabolism

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

247 Elimination

248 Following intravenous dosing with radiolabeled umeclidinium, mass balance showed 58% of the  
249 radiolabel in the feces and 22% in the urine. The excretion of the drug-related material in the  
250 feces following intravenous dosing indicated elimination in the bile. Following oral dosing to  
251 healthy male subjects, radiolabel recovered in feces was 92% of the total dose and that in urine  
252 was less than 1% of the total dose, suggesting negligible oral absorption. The effective half-life  
253 after once-daily dosing is 11 hours.

254 Special Populations

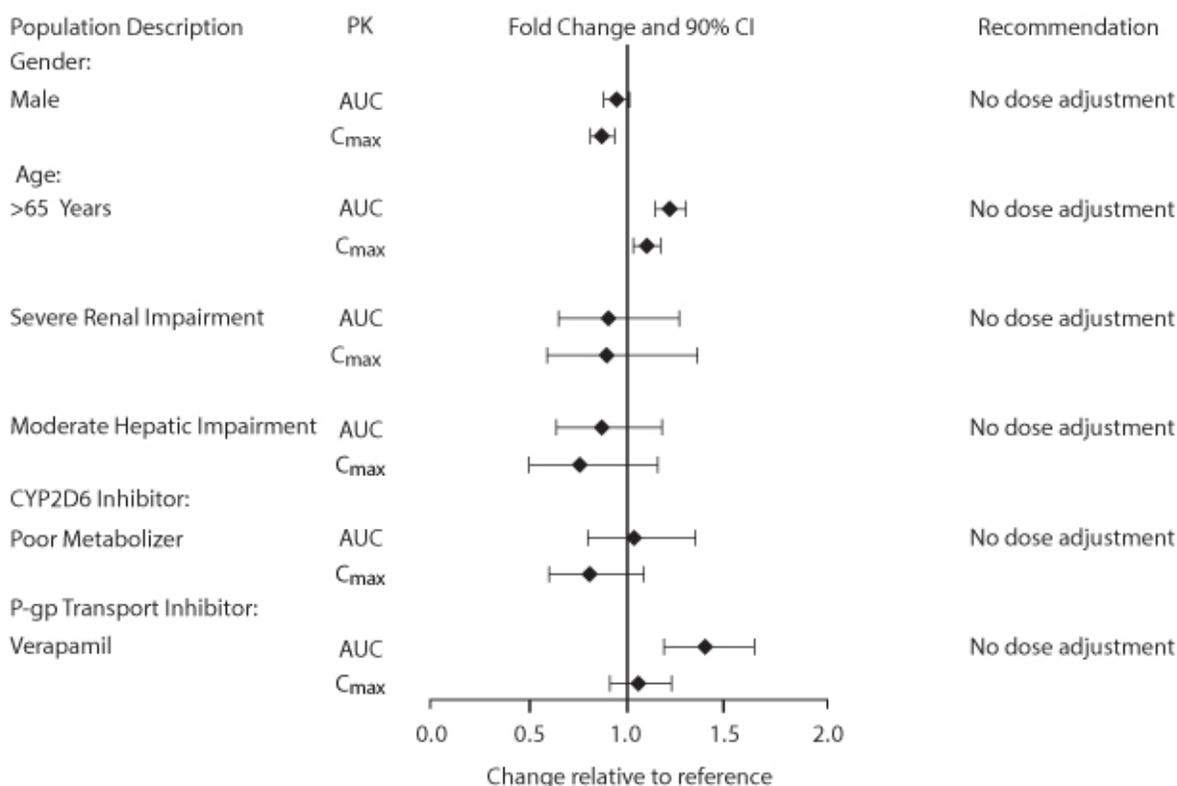
255 Population pharmacokinetic analysis showed no evidence of a clinically significant effect of age  
256 (40 to 93 years) (Figure 1), gender (69% male) (Figure 1), inhaled corticosteroid use (48%), or

257 weight (34 to 161 kg) on systemic exposure of umeclidinium. In addition, there was no evidence  
 258 of a clinically significant effect of race.

259 *Hepatic Impairment:* The impact of hepatic impairment on the pharmacokinetics of INCRUSE  
 260 ELLIPTA has been evaluated in subjects with moderate hepatic impairment (Child-Pugh score of  
 261 7-9). There was no evidence of an increase in systemic exposure to umeclidinium ( $C_{max}$  and  
 262 AUC) (Figure 1). There was no evidence of altered protein binding in subjects with moderate  
 263 hepatic impairment compared with healthy subjects. INCRUSE ELLIPTA has not been  
 264 evaluated in subjects with severe hepatic impairment.

265 *Renal Impairment:* The pharmacokinetics of INCRUSE ELLIPTA has been evaluated in subjects  
 266 with severe renal impairment (creatinine clearance less than 30 mL/min). There was no evidence  
 267 of an increase in systemic exposure to umeclidinium ( $C_{max}$  and AUC) (Figure 1). There was no  
 268 evidence of altered protein binding in subjects with severe renal impairment compared with  
 269 healthy subjects.

270 **Figure 1. Impact of Intrinsic and Extrinsic Factors on the Systemic Exposure of**  
 271 **Umeclidinium**



272

273 Drug Interactions

274 *Umeclidinium and P-glycoprotein Transporter:* Umeclidinium is a substrate of P-gp. The effect  
 275 of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state

276 pharmacokinetics of umeclidinium was assessed in healthy subjects. No effect on umeclidinium  
277  $C_{max}$  was observed; however, an approximately 1.4-fold increase in umeclidinium AUC was  
278 observed (Figure 1).

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

## 284 **13 NONCLINICAL TOXICOLOGY**

### 285 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

## 295 **14 CLINICAL STUDIES**

296 The safety and efficacy of umeclidinium 62.5 mcg were evaluated in 3 dose-ranging trials, 2  
297 placebo-controlled clinical trials (one 12-week trial and one 24-week trial), and a 12-month  
298 long-term safety trial. The efficacy of INCRUSE ELLIPTA is based primarily on the  
299 dose-ranging trials in 624 subjects with COPD and the 2 placebo-controlled confirmatory trials  
300 in 1,738 subjects with COPD.

301 The safety and efficacy of INCRUSE ELLIPTA in combination with an ICS/LABA were also  
302 evaluated in four 12-week clinical trials. The efficacy of INCRUSE ELLIPTA in combination  
303 with an ICS/LABA is based on 1,637 subjects with COPD.

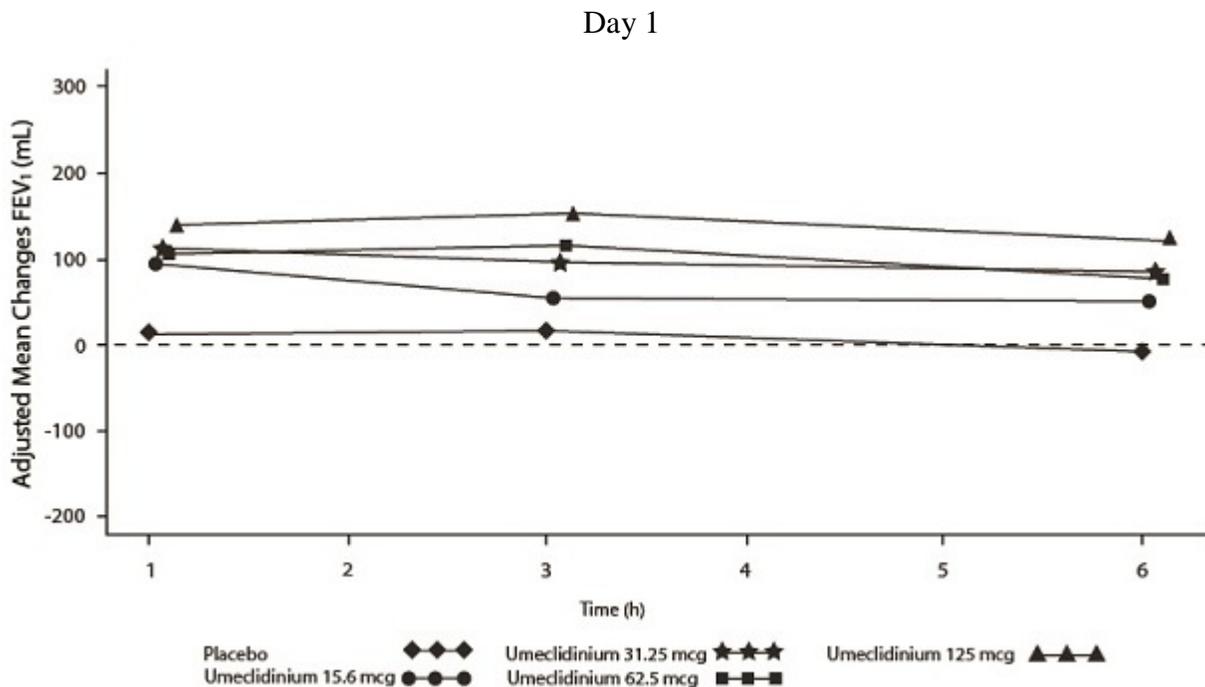
### 304 **14.1 Dose-Ranging Trials**

305 Dose selection for umeclidinium in COPD was supported by a 7-day, randomized, double-blind,  
306 placebo-controlled, crossover trial evaluating 4 doses of umeclidinium (15.6 to 125 mcg) or  
307 placebo dosed once daily in the morning in 163 subjects with COPD. A dose ordering was  
308 observed, with the 62.5- and 125-mcg doses demonstrating larger improvements in FEV<sub>1</sub> over  
309 24 hours compared with the lower doses of 15.6 and 31.25 mcg (Figure 2).

310 The differences in trough FEV<sub>1</sub> from baseline after 7 days for placebo and the 15.6-, 31.25-,  
 311 62.5-, and 125-mcg doses were -74 mL (95% CI: -118, -31), 38 mL (95% CI: -6, 83), 27 mL  
 312 (95% CI: -18, 72), 49 mL (95% CI: 6, 93), and 109 mL (95% CI: 65, 152), respectively. Two  
 313 additional dose-ranging trials in subjects with COPD demonstrated minimal additional benefit at  
 314 doses above 125 mcg. The dose-ranging results supported the evaluation of 2 doses of  
 315 umeclidinium, 62.5 and 125 mcg, in the confirmatory COPD trials to further assess dose  
 316 response.

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

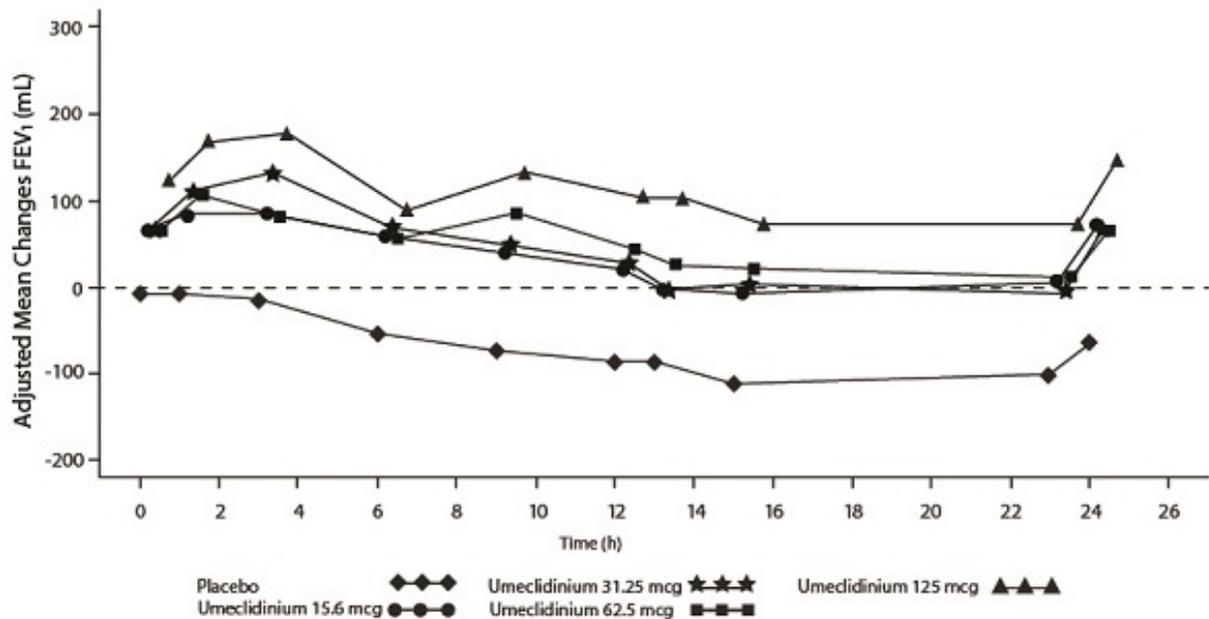
319 **Figure 2. Adjusted Mean Change from Baseline in Postdose Serial FEV<sub>1</sub> (mL) on Days 1**  
 320 **and 7**



322  
 323

324

Day 7



325

### 326 14.2 Maintenance Treatment: Confirmatory Trials

327 The clinical development program for INCRUSE ELLIPTA included 2 randomized,  
 328 double-blind, placebo-controlled, parallel-group trials in subjects with COPD designed to  
 329 evaluate the efficacy of INCRUSE ELLIPTA on lung function. Trial 1 was a 24-week  
 330 placebo-controlled trial, and Trial 2 was a 12-week placebo-controlled trial. These trials treated  
 331 subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of  
 332 smoking greater than or equal to 10 pack-years, had a post-albuterol FEV<sub>1</sub> less than or equal to  
 333 70% of predicted normal values, had a ratio of FEV<sub>1</sub>/FVC of less than 0.7, and had a Modified  
 334 Medical Research Council (mMRC) score greater than or equal to 2. Subjects in Trial 1 had a  
 335 mean age of 63 years and an average smoking history of 46 pack-years, with 50% identified as  
 336 current smokers. At screening, the mean postbronchodilator percent predicted FEV<sub>1</sub> was 47%  
 337 (range: 13% to 74%), the mean postbronchodilator FEV<sub>1</sub>/FVC ratio was 0.47 (range: 0.20 to  
 338 0.74), and the mean percent reversibility was 15% (range: -35% to 109%). Baseline  
 339 demographics and lung function for subjects in Trial 2 were similar to those in Trial 1.

340 Trial 1 evaluated umeclidinium 62.5 mcg and placebo. The primary endpoint was change from  
 341 baseline in trough (predose) FEV<sub>1</sub> at Day 169 (defined as the mean of the FEV<sub>1</sub> values obtained  
 342 at 23 and 24 hours after the previous dose on Day 168) compared with placebo. INCRUSE  
 343 ELLIPTA 62.5 mcg demonstrated a larger increase in mean change from baseline in trough  
 344 (predose) FEV<sub>1</sub> relative to placebo (Table 2). Similar results were obtained from Trial 2.

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

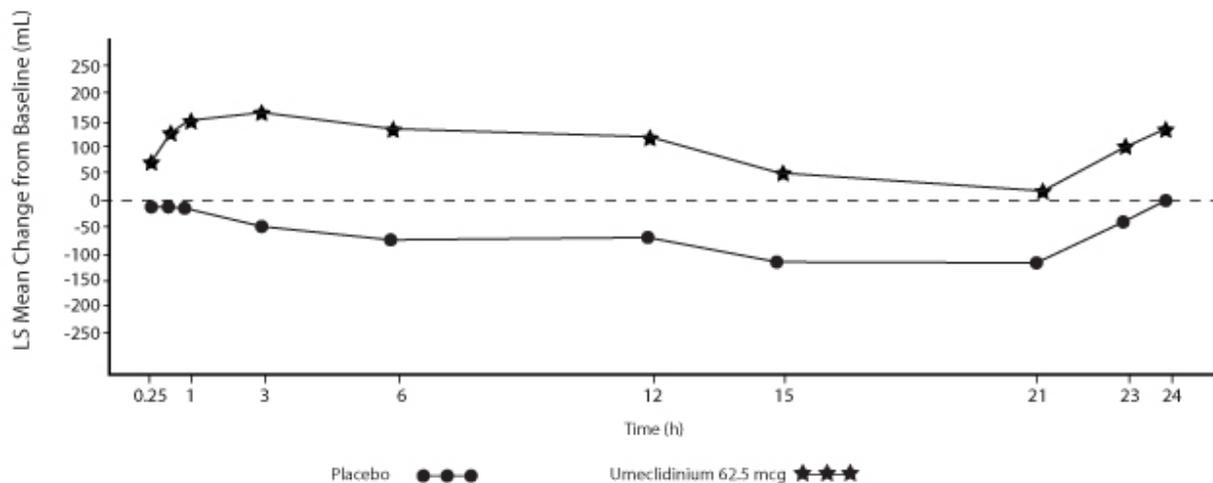
Treatment	n	Trough FEV <sub>1</sub> (mL) at Day 169
		Difference from Placebo (95% CI) n = 280
INCRUSE ELLIPTA	n = 418	115 (76, 155)

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

348 Serial spirometric evaluations throughout the 24-hour dosing interval were performed in a subset  
 349 of subjects (n = 54, umeclidinium 62.5 mcg; n = 36, placebo) at Days 1, 84, and 168 in Trial 1,  
 350 and for all patients at Days 1 and 84 in Trial 2. Results from Trial 1 at Day 1 and Day 168 are  
 351 shown in Figure 3.

352 **Figure 3. Least Squares (LS) Mean Change from Baseline in FEV<sub>1</sub> (mL) over Time**  
 353 **(0-24 h) on Days 1 and 168 (Trial 1 Subset Population)**

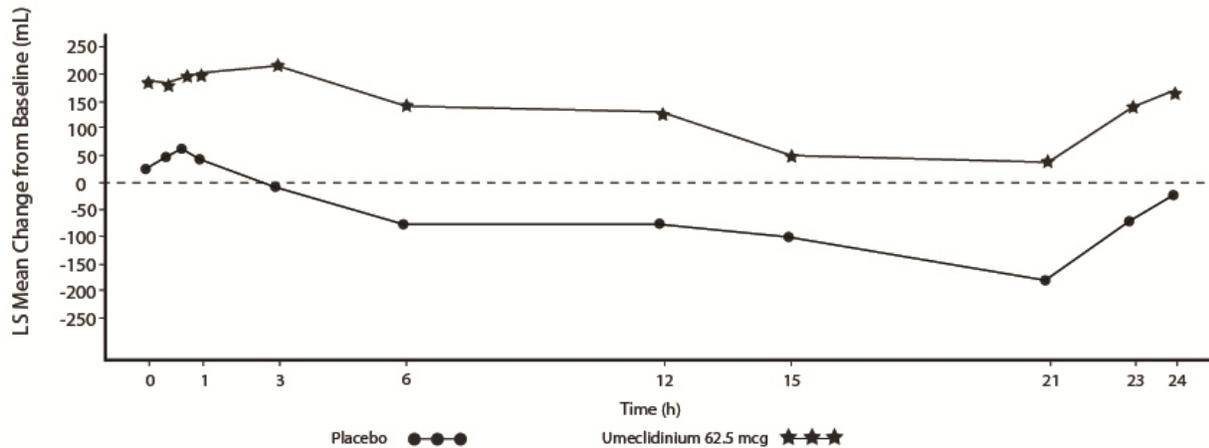
Day 1



355

356

Day 168



357

358 In Trial 1, the mean peak FEV<sub>1</sub> (over the first 6 hours relative to baseline) at Day 1 and at  
359 Day 168 for the group receiving umeclidinium 62.5 mcg compared with placebo was 126 and  
360 130 mL, respectively.

361 Health-related quality of life was measured using St. George's Respiratory Questionnaire  
362 (SGRQ). Umeclidinium demonstrated an improvement in mean SGRQ total score compared with  
363 placebo treatment at Day 168: -4.69 (95% CI: -7.07,-2.31). The proportion of patients with a  
364 clinically meaningful decrease (defined as a decrease of at least 4 units from baseline) at Week  
365 24 was greater for INCRUSE ELLIPTA 62.5 mcg (42%; 172/410) compared with placebo (31%;  
366 86/274).

### 367 14.3 Maintenance Treatment: Combination with an ICS/LABA Trials

368 The efficacy of INCRUSE ELLIPTA in combination with an ICS/LABA was evaluated in 4  
369 randomized, double-blind, parallel-group trials in subjects with COPD. These trials, all of similar  
370 study design, were of 12-weeks' treatment duration. Subjects were randomized to INCRUSE  
371 ELLIPTA 62.5 mcg + ICS/LABA or placebo + ICS/LABA. Entry criteria for subjects enrolled in  
372 these trials were similar to those described above in Section 14.2. The primary endpoint for these  
373 trials was change from baseline in trough (predose) FEV<sub>1</sub> at Day 85 (defined as the mean of the  
374 FEV<sub>1</sub> values obtained at 23 and 24 hours after the previous dose on Day 84). Baseline FEV<sub>1</sub> was  
375 measured while subjects were on background ICS/LABA.

#### 376 Combination with Fluticasone Furoate + Vilanterol

377 Trials 1 and 2 randomized subjects to INCRUSE ELLIPTA 62.5 mcg + FF/VI 100 mcg/25 mcg  
378 administered once daily or placebo + FF/VI 100 mcg/25 mcg administered once daily. Trial  
379 population demographics and results for Trials 1 and 2 were similar; therefore, only Trial 1  
380 results are presented below.

381 Subjects in Trial 1 across all treatment arms had a mean age of 64 years and an average smoking  
382 history of 50 pack-years, with 42% identified as current smokers. At screening, the mean

383 postbronchodilator percent predicted FEV<sub>1</sub> was 45% (range: 13% to 76%), the mean  
 384 postbronchodilator FEV<sub>1</sub>/FVC ratio was 0.48 (range: 0.22 to 0.70), and the mean percent  
 385 reversibility was 14% (range: -20% to 71%).

386 The primary endpoint was change from baseline in trough (predose) FEV<sub>1</sub> at Day 85 (defined as  
 387 the mean of the FEV<sub>1</sub> values obtained at 23 and 24 hours after the previous dose on Day 84)  
 388 compared with placebo (INCRUSE ELLIPTA + FF/VI vs. placebo + FF/VI). INCRUSE  
 389 ELLIPTA + FF/VI demonstrated a larger mean change from baseline in trough (predose) FEV<sub>1</sub>  
 390 relative to placebo + FF/VI (Table 3).

391 **Table 3. Least Squares Mean Change from Baseline in Trough FEV<sub>1</sub> (mL) at Day 85**  
 392 **in the Intent-to-Treat Population (Trial 1)**

Treatment	n	Trough FEV <sub>1</sub> (mL) at Day 85
		Difference from Placebo + FF/VI (95% CI) n = 206
INCRUSE ELLIPTA + FF/VI	n = 206	124 (93, 154)

393 FF/VI = Fluticasone furoate/vilanterol.

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

395 Combination with Fluticasone Propionate + Salmeterol

396 Trials 3 and 4 randomized subjects to INCRUSE ELLIPTA 62.5 mcg + FP/SAL  
 397 250 mcg/50 mcg or placebo + FP/SAL 250 mcg/50 mcg. The treatments with INCRUSE  
 398 ELLIPTA and placebo were administered once daily, while the FP/SAL treatment was  
 399 administered twice daily. Trial population demographics and results for Trials 3 and 4 were  
 400 similar; therefore, only Trial 3 results are presented below.

401 Subjects in Trial 3 across all treatment arms had a mean age of 63 years and an average smoking  
 402 history of 50 pack-years, with 54% identified as current smokers. At screening, the mean  
 403 postbronchodilator percent predicted FEV<sub>1</sub> was 47% (range: 12% to 70%), the mean  
 404 postbronchodilator FEV<sub>1</sub>/FVC ratio was 0.47 (range: 0.22 to 0.69), and the mean percent  
 405 reversibility was 16% (range: -36% to 79%).

406 The primary endpoint was change from baseline in trough (predose) FEV<sub>1</sub> at Day 85 (defined as  
 407 the mean of the FEV<sub>1</sub> values obtained at 23 and 24 hours after the previous dose on Day 84)  
 408 compared with placebo (INCRUSE ELLIPTA + FP/SAL vs. placebo + FP/SAL). INCRUSE  
 409 ELLIPTA + FP/SAL demonstrated a larger mean change from baseline in trough (predose) FEV<sub>1</sub>  
 410 relative to placebo + FP/SAL (Table 4).

411 **Table 4. Least Squares Mean Change from Baseline in Trough FEV<sub>1</sub> (mL) at Day 85**  
 412 **in the Intent-to-Treat Population (Trial 3)**

Treatment	n	Trough FEV <sub>1</sub> (mL) at Day 85
		Difference from Placebo + FP/SAL (95% CI) n = 205
INCRUSE ELLIPTA+FP/SAL	n = 204	147 (107, 187)

413 FP/SAL = Fluticasone propionate/salmeterol.

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

415 **16 HOW SUPPLIED/STORAGE AND HANDLING**

416 INCRUSE ELLIPTA is supplied as a disposable light grey and light green plastic inhaler  
 417 containing a foil strip with 30 blisters (NDC 0173-0873-10) or 7 blisters (institutional pack)  
 418 (NDC 0173-0873-06).

419 The inhaler is packaged in a moisture-protective foil tray with a desiccant and a peelable lid.

420 Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from  
 421 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place  
 422 away from direct heat or sunlight. Keep out of reach of children.

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

427 **17 PATIENT COUNSELING INFORMATION**

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

430 Not for Acute Symptoms

431 Inform patients that INCRUSE ELLIPTA is not meant to relieve acute symptoms of COPD and  
 432 extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an  
 433 inhaled, short-acting beta<sub>2</sub>-agonist such as albuterol. Provide patients with such medicine and  
 434 instruct them in how it should be used.

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

- 436 • Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonists
- 437 • Need for more inhalations than usual of inhaled, short-acting beta<sub>2</sub>-agonists
- 438 • Significant decrease in lung function as outlined by the physician

439 Tell patients they should not stop therapy with INCRUSE ELLIPTA without healthcare provider  
440 guidance since symptoms may recur after discontinuation.

441 Paradoxical Bronchospasm

442 As with other inhaled medicines, INCRUSE ELLIPTA can cause paradoxical bronchospasm. If  
443 paradoxical bronchospasm occurs, instruct patients to discontinue INCRUSE ELLIPTA.

444 Worsening of Narrow-angle Glaucoma

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

449 Worsening of Urinary Retention

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

453

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463 INC:xPI

## PATIENT INFORMATION

### **INCRUSE ELLIPTA [IN-cruise e-LIP-ta] (umeclidinium inhalation powder) for oral inhalation**

#### **What is INCRUSE ELLIPTA?**

- INCRUSE ELLIPTA is an anticholinergic medicine. Anticholinergic 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.
- INCRUSE ELLIPTA is a prescription medicine used to treat chronic obstructive pulmonary disease (COPD). COPD is a long-term (chronic) lung disease that includes chronic bronchitis, emphysema, or both. INCRUSE ELLIPTA is used long term as 1 inhalation 1 time each day to improve symptoms of COPD for better breathing.
- **INCRUSE ELLIPTA is not used to relieve sudden breathing problems** and will not replace a rescue inhaler.
- INCRUSE ELLIPTA should not be used in children. It is not known if INCRUSE ELLIPTA is safe and effective in children.

#### **Do not use INCRUSE ELLIPTA if you:**

- have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- are allergic to umeclidinium or any of the ingredients in INCRUSE ELLIPTA. See the end of this leaflet for a complete list of ingredients in INCRUSE ELLIPTA.

#### **Before using INCRUSE ELLIPTA, tell your healthcare provider about all of your medical conditions, including if you:**

- have heart problems.
- have eye problems such as glaucoma. INCRUSE ELLIPTA may make your glaucoma worse.
- have prostate or bladder problems, or problems passing urine. INCRUSE ELLIPTA may make these problems worse.
- are allergic to any of the ingredients in INCRUSE ELLIPTA, any other medicines, or food products. See “What are the ingredients in INCRUSE ELLIPTA?” below for a complete list of ingredients.
- are pregnant or plan to become pregnant. It is not known if INCRUSE ELLIPTA may harm your unborn baby.
- are breastfeeding. It is not known if the medicine in INCRUSE ELLIPTA passes into your breast milk and if it 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. INCRUSE 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 INCRUSE ELLIPTA?**

**Read the step-by-step instructions for using INCRUSE ELLIPTA at the end of this Patient Information.**

- **Do not** use INCRUSE ELLIPTA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.

- Use INCRUSE ELLIPTA exactly as your healthcare provider tells you to use it. **Do not** use INCRUSE ELLIPTA more often than prescribed.
- Use 1 inhalation of INCRUSE ELLIPTA 1 time each day. Use INCRUSE ELLIPTA at the same time each day.
- If you miss a dose of INCRUSE 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 1 time.
- If you take too much INCRUSE 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 an anticholinergic for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are anticholinergic medicines.
- **Do not** stop using INCRUSE ELLIPTA, even if you are feeling better, unless your healthcare provider tells you to.
- Talk to your healthcare provider right away if you stop using INCRUSE ELLIPTA.
- **INCRUSE ELLIPTA does not relieve sudden symptoms of COPD and you should not take extra doses of INCRUSE ELLIPTA to relieve these 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 of INCRUSE ELLIPTA?**

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

- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop taking INCRUSE ELLIPTA and call your healthcare provider right away.
- **serious allergic reactions (anaphylaxis).** Stop using INCRUSE ELLIPTA and call your healthcare provider or go to the nearest emergency room right away if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - severe itching
  - swelling of your face, lips, mouth, or tongue
  - breathing problems
- **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 healthcare provider right away before taking another dose.

- **urinary retention.** People who take INCRUSE 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 INCRUSE ELLIPTA, and call your healthcare provider right away before taking another dose.

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

- upper respiratory tract infection
- muscle pain
- stuffy or runny nose
- tooth pain
- cough
- stomach pain
- mouth and throat pain
- bruising or dark areas of skin
- joint pain
- fast or irregular heartbeat
- change in taste

These are not all the possible side effects of INCRUSE ELLIPTA.

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 INCRUSE ELLIPTA?**

- Store INCRUSE 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 INCRUSE ELLIPTA in the unopened foil tray and only open when ready for use.
- Safely throw away INCRUSE 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 INCRUSE ELLIPTA and all medicines out of the reach of children.**

**General information about the safe and effective use of INCRUSE ELLIPTA.**

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

You can ask your healthcare provider or pharmacist for information about INCRUSE ELLIPTA that was written for health professionals.

**What are the ingredients in INCRUSE ELLIPTA?**

Active ingredient: umeclidinium

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



For more information about INCRUSE ELLIPTA, call 1-888-825-5249 or visit our website at [www.INCRUSE.com](http://www.INCRUSE.com).  
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This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: Month 2017

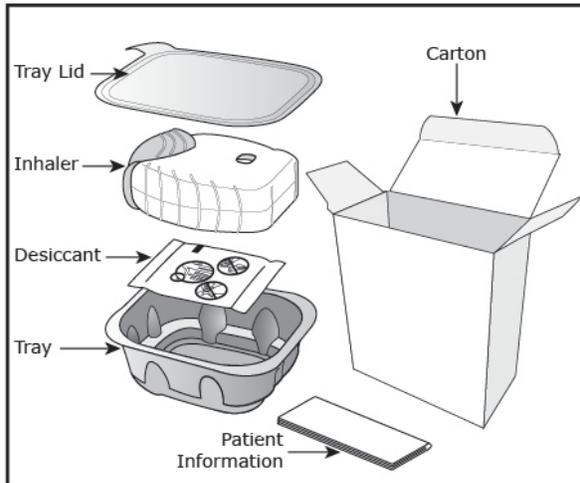
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<p><b>INSTRUCTIONS FOR USE</b></p> <p><b>INCRUSE ELLIPTA [IN-cruise e-LIP-ta]</b></p> <p><b>(umeclidinium inhalation powder)</b></p> <p><b>for oral inhalation</b></p>
<p><b>Read this before you start:</b></p> <ul style="list-style-type: none"><li>• <b>If you open and close the cover without inhaling the medicine, you will lose the dose.</b></li><li>• <b>The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.</b></li></ul>

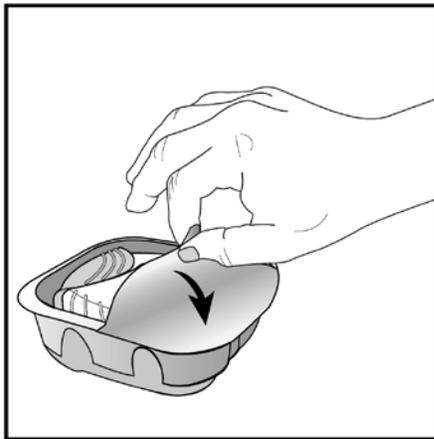
- It is not possible to accidentally take a double dose or an extra dose in 1 inhalation.

#### Your INCRUSE ELLIPTA inhaler

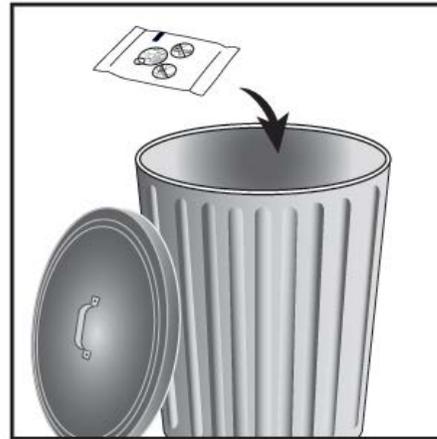


#### How to use your inhaler

- INCRUSE 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 breathe in (inhale). Throw it away in the household trash out of reach of children and pets. **See Figure B.**



**Figure A**



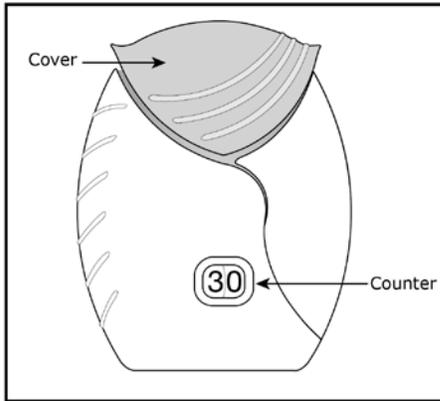
**Figure B**

#### 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.**

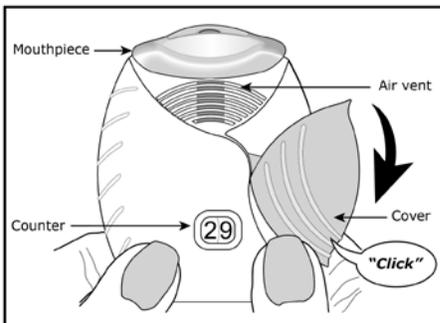


**Figure C**

- 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.**



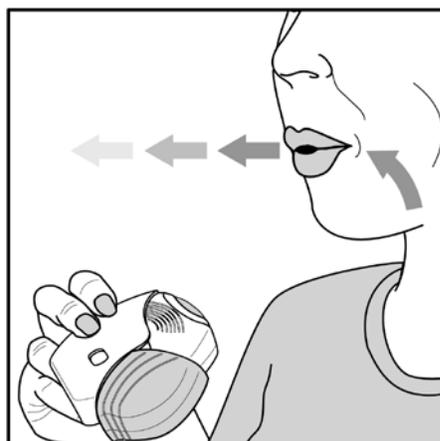
**Figure D**

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

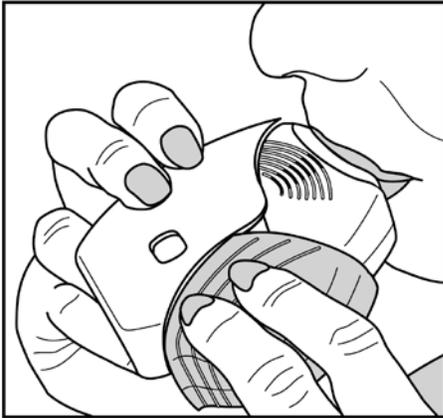
- Slide the cover down to show (expose) the mouthpiece. You should hear a “click.” The counter will count down by 1 number. You do not need to shake this kind of inhaler. **Your inhaler is now ready to use.**
- If the counter does not count down as you hear the click, the inhaler will not deliver the 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.



**Figure E**

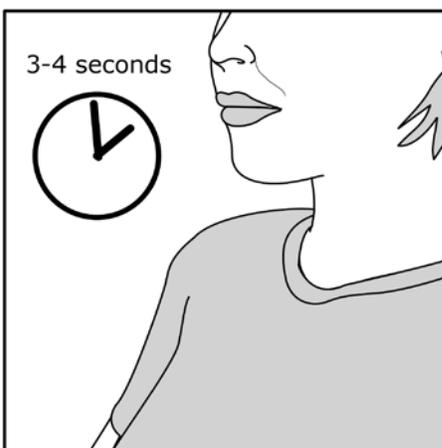


**Figure F**

Do not block the air vent with your fingers.



**Figure G**



**Figure H**

**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. **See Figure G.**

- **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.**

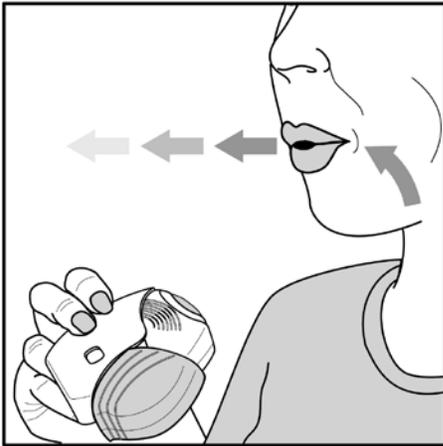


Figure I

**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.

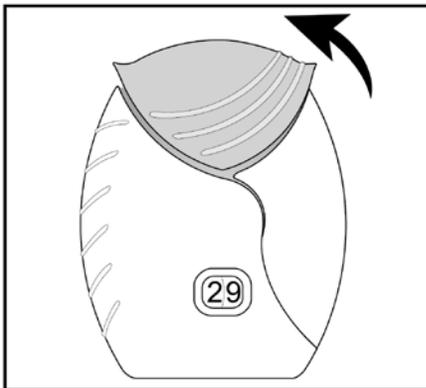


Figure J

**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?**

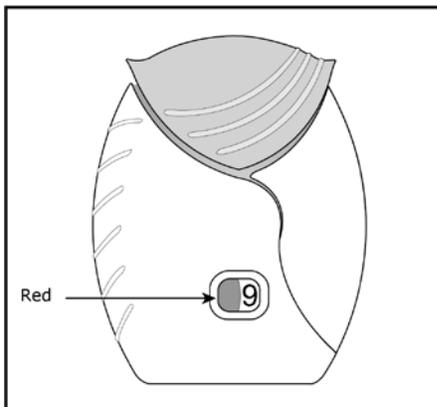


Figure K

- **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.



For more information about INCRUSE ELLIPTA or how to use your inhaler, call 1-888-825-5249 or visit our website at [www.INCRUSE.com](http://www.INCRUSE.com).

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