

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 USE
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 double-foil blister strip of powder formulation for oral inhalation. Each blister contains umeclidinium 62.5 mcg. (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 physician 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 physician immediately if symptoms occur. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 2\%$ 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: XX/20XX

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1 FULL PRESCRIBING INFORMATION

2 1 INDICATIONS AND USAGE

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

6 2 DOSAGE AND ADMINISTRATION

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

9 INCRUSE ELLIPTA should be taken 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
15 double-foil blister strip with 30 blisters containing powder intended for oral inhalation only.
16 Each blister contains umeclidinium 62.5 mcg. An institutional pack containing a blister strip with
17 7 blisters is also available.

18 4 CONTRAINDICATIONS

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

- 20 • Severe hypersensitivity to milk proteins [*see Warnings and Precautions (5.3)*]
- 21 • Hypersensitivity to umeclidinium or any of the excipients [*see Warnings and Precautions*
22 (*5.3*), *Description (11)*]

23 5 WARNINGS AND PRECAUTIONS

24 5.1 Deterioration of Disease and Acute Episodes

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

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

33 COPD may deteriorate acutely over a period of hours or chronically over several days or
34 longer. If INCRUSE ELLIPTA no longer controls symptoms of bronchoconstriction; the
35 patient's inhaled, short-acting beta₂-agonist becomes less effective; or the patient needs more
36 short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this

37 setting a re-evaluation of the patient and the COPD treatment regimen should be undertaken at
38 once. Increasing the daily dose of INCRUSE ELLIPTA beyond the recommended dose is not
39 appropriate in this situation.

40 **5.2 Paradoxical Bronchospasm**

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

46 **5.3 Hypersensitivity Reactions**

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

51 **5.4 Worsening of Narrow-Angle Glaucoma**

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

57 **5.5 Worsening of Urinary Retention**

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

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
70 rates observed in the clinical trials of a drug cannot be directly compared with rates in the
71 clinical trials of another drug and may not reflect the rates observed in practice.

72 A total of 1,663 subjects with COPD across 8 clinical trials (mean age: 62.7 years; 89%
73 white; 65% male across all treatments, including placebo) received at least 1 inhalation dose of
74 umeclidinium at doses of 62.5 or 125 mcg. In the 4 randomized, double-blind, placebo- or
75 active-controlled efficacy clinical trials, 1,185 subjects received umeclidinium for up to 24

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

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

81

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

Adverse Reaction	INCRUSE ELLIPTA (n = 487) %	Placebo (n = 348) %
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

85 Other adverse reactions with INCRUSE ELLIPTA observed with an incidence less than
 86 1% but more common than placebo included atrial fibrillation.

87 In a long-term safety trial, 336 subjects (n = 227 umeclidinium 125 mcg, n = 109
 88 placebo) were treated for up to 52 weeks with umeclidinium 125 mcg or placebo. The
 89 demographic and baseline characteristics of the long-term safety trial were similar to those of the
 90 efficacy trials described above. Adverse reactions that occurred with a frequency greater than or
 91 equal to 1% in subjects receiving umeclidinium 125 mcg that exceeded that in placebo in this

92 trial were: nasopharyngitis, upper respiratory tract infection, urinary tract infection, pharyngitis,
93 pneumonia, lower respiratory tract infection, rhinitis, supraventricular tachycardia,
94 supraventricular extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness,
95 sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea,
96 dyspepsia, diarrhea, rash, depression, and vertigo.

97 **7 DRUG INTERACTIONS**

98 **7.1 Anticholinergics**

99 There is potential for an additive interaction with concomitantly used anticholinergic
100 medicines. Therefore, avoid coadministration of INCRUSE ELLIPTA with other
101 anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects
102 [*see Warnings and Precautions (5.4, 5.5), Adverse Reactions (6)*].

103 **8 USE IN SPECIFIC POPULATIONS**

104 **8.1 Pregnancy**

105 Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled
106 trials with INCRUSE ELLIPTA in pregnant women. Because animal reproduction studies are
107 not always predictive of human response, INCRUSE ELLIPTA should be used during pregnancy
108 only if the potential benefit justifies the potential risk to the fetus. Women should be advised to
109 contact their physicians if they become pregnant while taking INCRUSE ELLIPTA.

110 There was no evidence of teratogenic effects in rats and rabbits at approximately 50 and
111 200 times, respectively, the MRHDID (maximum recommended human daily inhaled dose) in
112 adults (on an AUC basis at maternal inhaled doses up to 278 mcg/kg/day in rats and maternal
113 subcutaneous doses up to 180 mcg/kg/day in rabbits).

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

117 **8.2 Labor and Delivery**

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

121 **8.3 Nursing Mothers**

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

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

131 **8.4 Pediatric Use**

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

134 **8.5 Geriatric Use**

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

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

142 **8.6 Hepatic Impairment**

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

147 **8.7 Renal Impairment**

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

152 **10 OVERDOSAGE**

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

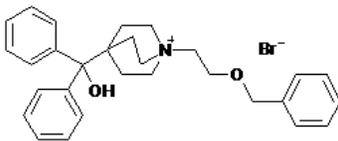
154 High doses of umeclidinium may lead to anticholinergic signs and symptoms. However,
155 there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up
156 to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in
157 subjects with COPD.

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

160 **11 DESCRIPTION**

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

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



165

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

169 INCRUSE ELLIPTA is a light grey and light green plastic inhaler containing a double-
170 foil blister strip. Each blister on the strip contains a white powder mix of micronized
171 umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg of umeclidinium), magnesium stearate
172 (75 mcg), and lactose monohydrate (to 12.5 mg). The lactose monohydrate contains milk
173 proteins. After the inhaler is activated, the powder within the blister is exposed and ready for
174 dispersion into the airstream created by the patient inhaling through the mouthpiece.

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

177 In adult subjects with obstructive lung disease and severely compromised lung function
178 (COPD with forced expiratory volume in 1 second/forced vital capacity [FEV₁/FVC] less than
179 70% and FEV₁ less than 30% predicted or FEV₁ less than 50% predicted plus chronic respiratory
180 failure), mean peak inspiratory flow through the ELLIPTA inhaler was 66.5 L/min (range: 43.5
181 to 81.0 L/min).

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

184 **12 CLINICAL PHARMACOLOGY**

185 **12.1 Mechanism of Action**

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

195 **12.2 Pharmacodynamics**

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

200 **12.3 Pharmacokinetics**

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

202 Absorption: Umeclidinium plasma levels may not predict therapeutic effect. Following
203 inhaled administration of umeclidinium in healthy subjects, C_{max} occurred at 5 to 15 minutes.

204 Umeclidinium is mostly absorbed from the lung after inhaled doses with minimum contribution

205 from oral absorption. Following repeat dosing of inhaled INCRUSE ELLIPTA, steady state was
206 achieved within 14 days with 1.8-fold accumulation.

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

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

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

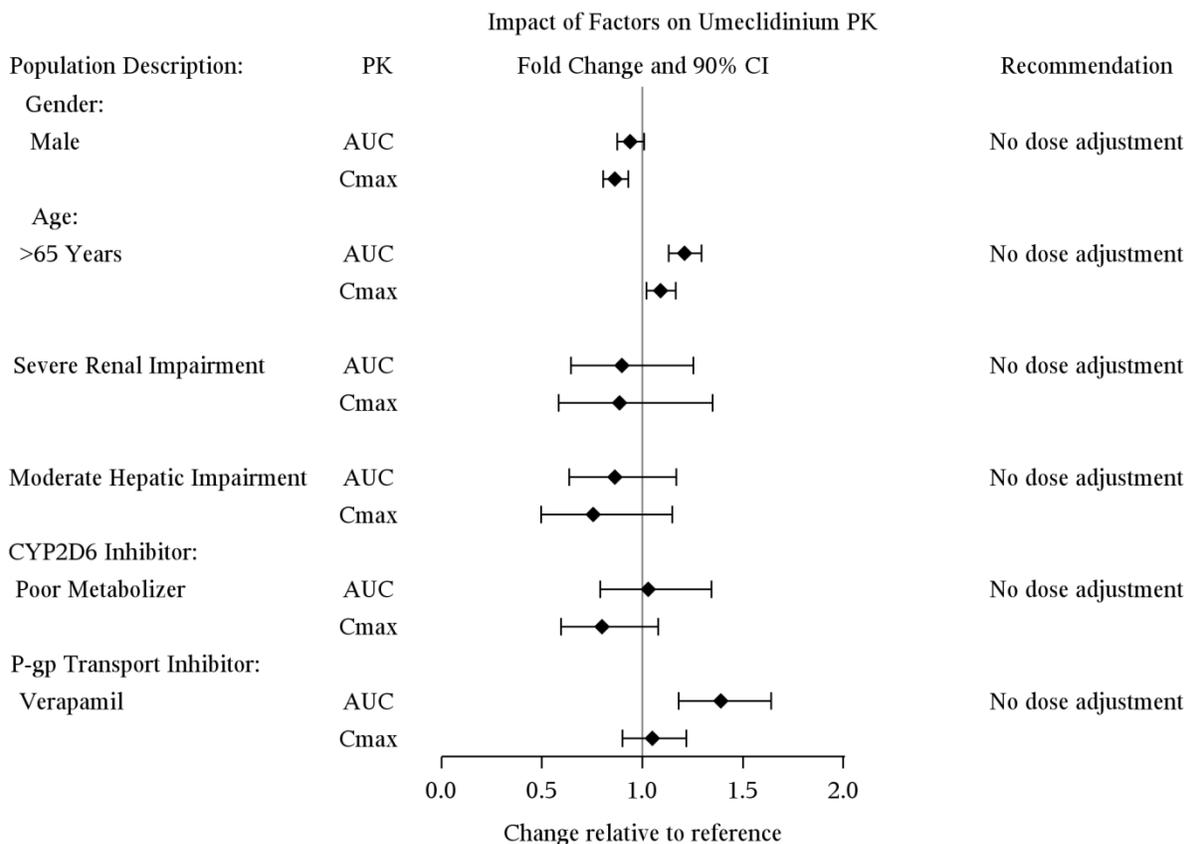
221 Special Populations: Population pharmacokinetic analysis showed no evidence of a
222 clinically significant effect of age (40 to 93 years) (see Figure 1), gender (69% male) (see Figure
223 1), inhaled corticosteroid use (48%), or weight (34 to 161 kg) on systemic exposure of
224 umeclidinium. In addition, there was no evidence of a clinically significant effect of race.

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

231 Renal Impairment: The pharmacokinetics of INCRUSE ELLIPTA has been
232 evaluated in subjects with severe renal impairment (creatinine clearance less than 30 mL/min).
233 There was no evidence of an increase in systemic exposure to umeclidinium (C_{max} and AUC)
234 (see Figure 1). There was no evidence of altered protein binding in subjects with severe renal
235 impairment compared with healthy subjects.

236

237 **Figure 1. Impact of Intrinsic and Extrinsic Factors on the Systemic Exposure of**
 238 **Umeclidinium**



239
 240
 241 **Drug Interactions: Umeclidinium and P-glycoprotein Transporter:** Umeclidinium is
 242 a substrate of P-gp. The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once
 243 daily) on the steady-state pharmacokinetics of umeclidinium was assessed in healthy subjects.
 244 No effect on umeclidinium C_{max} was observed; however, an approximately 1.4-fold increase in
 245 umeclidinium AUC was observed (see Figure 1).

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

251 **13 NONCLINICAL TOXICOLOGY**

252 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

262 **14 CLINICAL STUDIES**

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

268 **14.1 Dose-Ranging Trials**

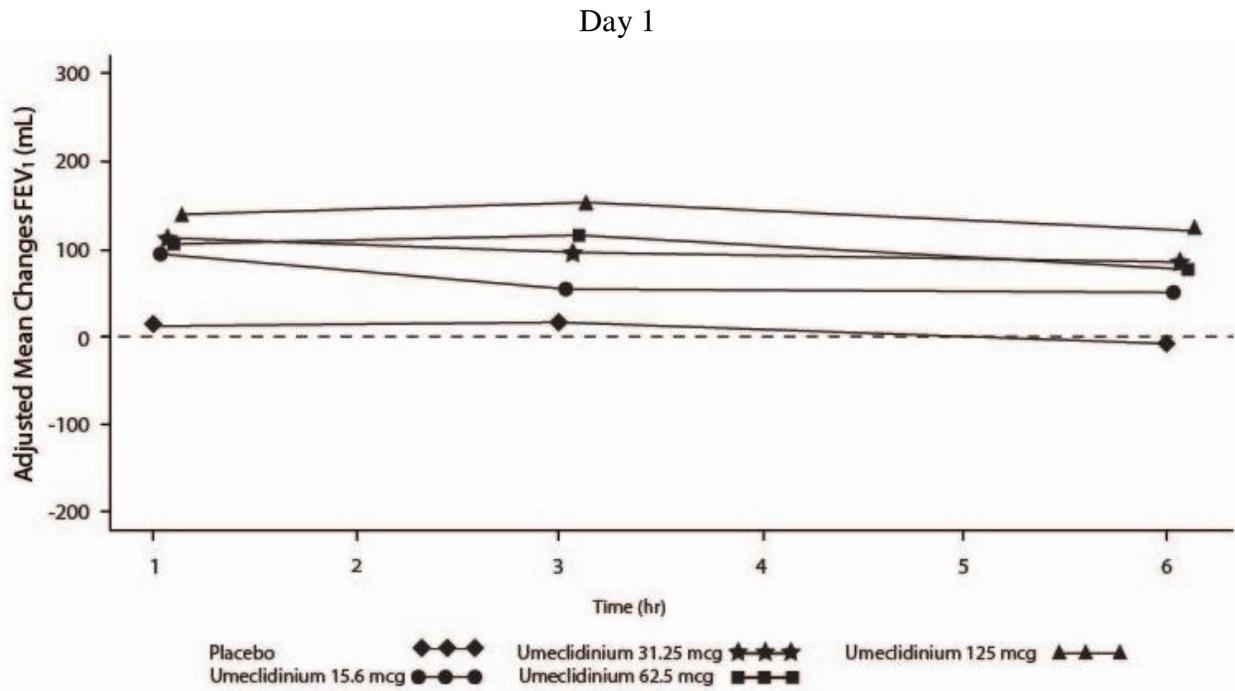
269 Dose selection for umeclidinium in COPD was supported by a 7-day, randomized,
270 double-blind, placebo-controlled, crossover trial evaluating 4 doses of umeclidinium (15.6 to 125
271 mcg) or placebo dosed once daily in the morning in 163 subjects with COPD. A dose ordering
272 was observed, with the 62.5- and 125-mcg doses demonstrating larger improvements in FEV₁
273 over 24 hours compared with the lower doses of 15.6 and 31.25 mcg (Figure 2).

274 The differences in trough FEV₁ from baseline after 7 days for placebo and the 15.6-,
275 31.25-, 62.5-, and 125-mcg doses were -74 mL (95% CI: -118, -31), 38 mL (95% CI: -6, 83), 27
276 mL (95% CI: -18, 72), 49 mL (95% CI: 6, 93), and 109 mL (95% CI: 65, 152), respectively. Two
277 additional dose-ranging trials in subjects with COPD demonstrated minimal additional benefit at
278 doses above 125 mcg. The dose-ranging results supported the evaluation of 2 doses of
279 umeclidinium, 62.5 and 125 mcg, in the confirmatory COPD trials to further assess dose
280 response.

281 Evaluations of dosing interval by comparing once- and twice-daily dosing supported
282 selection of a once-daily dosing interval for further evaluation in the confirmatory COPD trials.
283

284 **Figure 2. Adjusted Mean Change From Baseline in Post-Dose Serial FEV₁ (mL) on Days 1**
 285 **and 7**

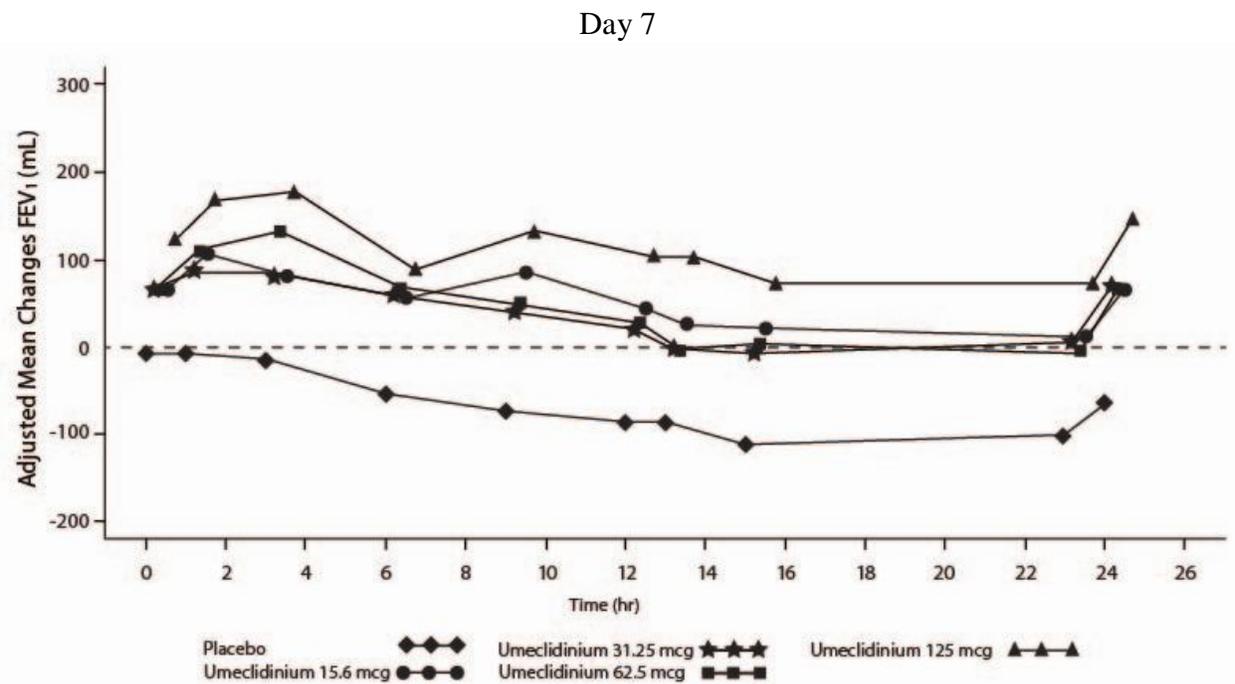
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292 **14.2 Confirmatory Trials**

293 The clinical development program for INCRUSE ELLIPTA included 2 randomized,
 294 double-blind, placebo-controlled, parallel-group trials in subjects with COPD designed to

295 evaluate the efficacy of INCRUSE ELLIPTA on lung function. Trial 1 was a 24-week placebo-
 296 controlled trial, and Trial 2 was a 12-week placebo-controlled trial. These trials treated subjects
 297 that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking
 298 equal to or greater than 10 pack-years, had a post-albuterol FEV₁ less than or equal to 70% of
 299 predicted normal values, had a ratio of FEV₁/FVC of less than 0.7, and had a Modified Medical
 300 Research Council (mMRC) score equal to or greater than 2. Subjects in Trial 1 had a mean age
 301 of 63 years and an average smoking history of 46 pack-years, with 50% identified as current
 302 smokers. At screening, the mean post-bronchodilator percent predicted FEV₁ was 47% (range:
 303 13% to 74%), the mean post-bronchodilator FEV₁/FVC ratio was 0.47 (range: 0.20 to 0.74), and
 304 the mean percent reversibility was 15% (range: -35% to 109%). Baseline demographics and lung
 305 function for subjects in Trial 2 were similar to those in Trial 1.

306 Trial 1 evaluated umeclidinium 62.5 mcg and placebo. The primary endpoint was change
 307 from baseline in trough (predose) FEV₁ at Day 169 (defined as the mean of the FEV₁ values
 308 obtained at 23 and 24 hours after the previous dose on Day 168) compared with placebo.
 309 INCRUSE ELLIPTA 62.5 mcg demonstrated a larger increase in mean change from baseline in
 310 trough (predose) FEV₁ relative to placebo (see Table 2). Similar results were obtained from Trial
 311 2.

312

313 **Table 2. Least Squares (LS) Mean Change From Baseline in Trough FEV₁ (mL) at Day**
 314 **169 in the Intent-to-Treat Population (Trial 1)**

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

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

316

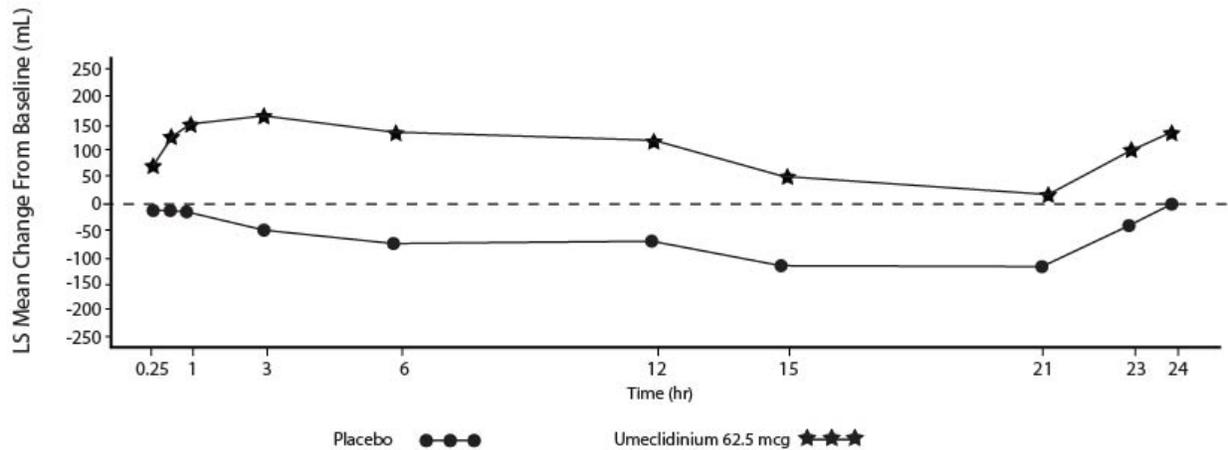
317 Serial spirometric evaluations throughout the 24-hour dosing interval were performed in
 318 a subset of subjects (n = 54, umeclidinium 62.5 mcg; n = 36, placebo) at Days 1, 84, and 168 in
 319 Trial 1, and for all patients at Days 1 and 84 in Trial 2. Results from Trial 1 at Day 1 and Day
 320 168 are shown in Figure 3.

321

322 **Figure 3. Least Squares (LS) Mean Change From Baseline in FEV₁ (mL) Over Time (0-24**
 323 **hr) on Days 1 and 168 (Trial 1 Subset Population)**

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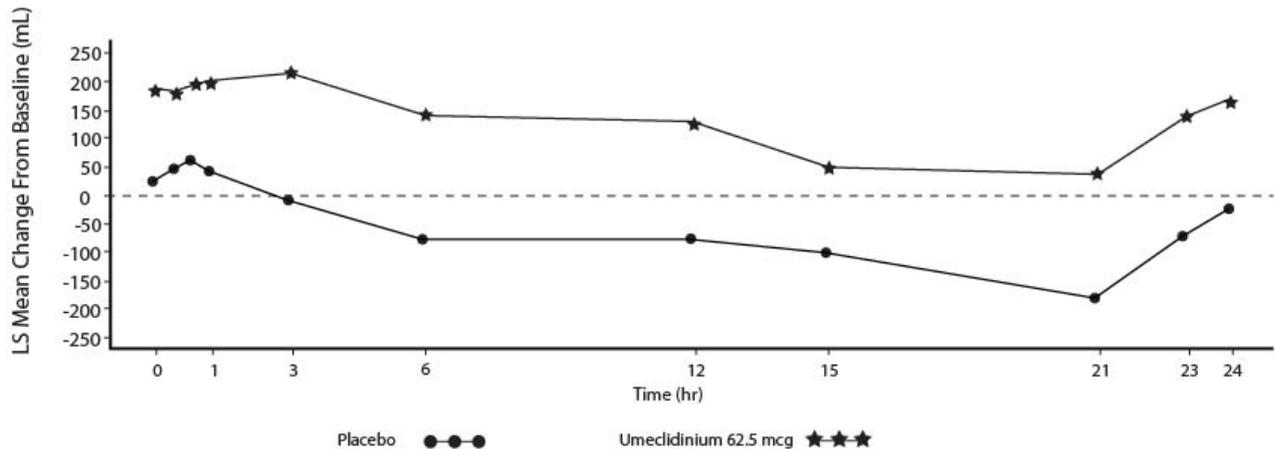
Day 1



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Day 168



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336

In Trial 1, the mean peak FEV₁ (over the first 6 hours relative to baseline) at Day 1 and at Day 168 for the group receiving umeclidinium 62.5 mcg compared with placebo was 126 and 130 mL, respectively.

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

337

16 HOW SUPPLIED/STORAGE AND HANDLING

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342

INCRUSE ELLIPTA is supplied as a disposable light grey and light green plastic inhaler containing a double-foil blister strip with 30 blisters. The inhaler is packaged in a moisture-protective foil tray with a desiccant and a peelable lid (NDC 0173-0873-10).

INCRUSE ELLIPTA is also supplied in an institutional pack of a disposable light grey and light green plastic inhaler containing a double-foil blister strip with 7 blisters. The inhaler is

343 packaged in a moisture-protective foil tray with a desiccant and a peelable lid (NDC 0173-0873-
344 06).

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

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

352 **17 PATIENT COUNSELING INFORMATION**

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

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

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

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

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

365 Paradoxical Bronchospasm: As with other inhaled medicines, INCRUSE ELLIPTA
366 can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to
367 discontinue INCRUSE ELLIPTA.

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

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

376
377 INCRUSE is a trademark and ELLIPTA is a registered trademark of the GSK group of
378 companies.

379

380



381
382 GlaxoSmithKline
383 Research Triangle Park, NC 27709

384
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386
387 INC:xPI

389 Patient Information

390 **INCRUSE™ [IN-cruise] ELLIPTA® [e-LIP-ta]** 391 **(umeclidinium inhalation powder)**

392
393 Read the Patient Information that comes with INCRUSE ELLIPTA before you start
394 using it and each time you get a refill. There may be new information. This Patient
395 Information does not take the place of talking to your healthcare provider about
396 your medical condition or treatment.

397 398 **What is INCRUSE ELLIPTA?**

399 INCRUSE ELLIPTA is an anticholinergic medicine. Anticholinergic medicines help the
400 muscles around the airways in your lungs stay relaxed to prevent symptoms such
401 as wheezing, cough, chest tightness, and shortness of breath. These symptoms can
402 happen when the muscles around the airways tighten. This makes it hard to
403 breathe.

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

- 408 • **INCRUSE ELLIPTA is not for use to treat sudden symptoms of COPD.**
409 Always have a rescue inhaler (an inhaled, short-acting bronchodilator) with you
410 to treat sudden symptoms. If you do not have a rescue inhaler, contact your
411 healthcare provider to have one prescribed for you.
- 412 • INCRUSE ELLIPTA should not be used in children. It is not known if INCRUSE
413 ELLIPTA is safe and effective in children.

414 415 **Who should not use INCRUSE ELLIPTA?**

416 Do not use INCRUSE ELLIPTA if you:

- 417 • have a severe allergy to milk proteins. Ask your healthcare provider if you are
418 not sure.
419 • are allergic to umeclidinium or any of the ingredients in INCRUSE ELLIPTA. See
420 “What are the ingredients in INCRUSE ELLIPTA?” below for a complete list of
421 ingredients.
422

423 **What should I tell my healthcare provider before using INCRUSE ELLIPTA?**

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

- 426 • have heart problems.
427 • have eye problems such as glaucoma. INCRUSE ELLIPTA may make your
428 glaucoma worse.
429 • have prostate or bladder problems, or problems passing urine. INCRUSE
430 ELLIPTA may make these problems worse.
431 • are allergic to any of the ingredients in INCRUSE ELLIPTA, any other medicines,
432 or food products. See “What are the ingredients in INCRUSE ELLIPTA?” below for
433 a complete list of ingredients.
434 • have any other medical conditions.
435 • are pregnant or planning to become pregnant. It is not known if INCRUSE
436 ELLIPTA may harm your unborn baby.
437 • are breastfeeding. It is not known if the medicine in INCRUSE ELLIPTA passes
438 into your milk and if it can harm your baby.

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

443 Especially tell your healthcare provider if you take:

- 444 • anticholinergics (including tiotropium, ipratropium, acclidinium)
445 • atropine

446 Know the medicines you take. Keep a list of them to show your healthcare provider
447 and pharmacist when you get a new medicine.
448

449 **How should I use INCRUSE ELLIPTA?**

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

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

- 454 • Use INCRUSE ELLIPTA exactly as your healthcare provider tells you to use it. **Do**
455 **not** use INCRUSE ELLIPTA more often than prescribed.
- 456 • Use 1 inhalation of INCRUSE ELLIPTA 1 time each day. Use INCRUSE ELLIPTA at
457 the same time each day.
- 458 • If you miss a dose of INCRUSE ELLIPTA, take it as soon as you remember. Do
459 not take more than 1 inhalation each day. Take your next dose at your usual
460 time. Do not take 2 doses at one time.
- 461 • If you take too much INCRUSE ELLIPTA, call your healthcare provider or go to
462 the nearest hospital emergency room right away if you have any unusual
463 symptoms, such as worsening shortness of breath, chest pain, increased heart
464 rate, or shakiness.
- 465 • **Do not use other medicines that contain an anticholinergic for any**
466 **reason.** Ask your healthcare provider or pharmacist if any of your other
467 medicines are anticholinergic medicines.
- 468 • Do not stop using INCRUSE ELLIPTA unless told to do so by your healthcare
469 provider because your symptoms might get worse. Your healthcare provider will
470 change your medicines as needed.
- 471 • **INCRUSE ELLIPTA does not relieve sudden symptoms.** Always have a
472 rescue inhaler with you to treat sudden symptoms. If you do not have a rescue
473 inhaler, call your healthcare provider to have one prescribed for you.
- 474 • Call your healthcare provider or get medical care right away if:
475
 - your breathing problems get worse
 - 476 • you need to use your rescue inhaler more often than usual
 - 477 • your rescue inhaler does not work as well to relieve your symptoms
478

479 **What are the possible side effects with INCRUSE ELLIPTA?**

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

- 481 • **sudden breathing problems immediately after inhaling your medicine.** If
482 you have sudden breathing problems immediately after inhaling your medicine,
483 stop taking INCRUSE ELLIPTA and call your doctor right away.
- 484 • **serious allergic reactions.** Call your healthcare provider or get emergency
485 medical care if you get any of the following symptoms of a serious allergic
486 reaction:
 - 487 • rash
 - 488 • hives
 - 489 • swelling of the face, mouth, and tongue

- 490 • breathing problems
- 491 • **new or worsened eye problems including acute narrow-angle glaucoma.**
- 492 Acute narrow-angle glaucoma can cause permanent loss of vision if not treated.
- 493 Symptoms of acute narrow-angle glaucoma may include:
- 494 • eye pain or discomfort
- 495 • nausea or vomiting
- 496 • blurred vision
- 497 • seeing halos or bright colors around lights
- 498 • red eyes

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

- 501 • **urinary retention.** People who take INCRUSE ELLIPTA may develop new or
502 worse urinary retention. Symptoms of urinary retention may include:
- 503 • difficulty urinating
- 504 • painful urination
- 505 • urinating frequently
- 506 • urination in a weak stream or drips

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

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

- 510 • upper respiratory infection
- 511 • stuffy or runny nose
- 512 • cough
- 513 • sore throat
- 514 • joint pain
- 515 • muscle pain
- 516 • tooth pain
- 517 • stomach pain
- 518 • bruising or dark areas of skin
- 519 • fast or irregular heartbeat

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

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

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

526

527 **How do I store INCRUSE ELLIPTA?**

- 528 • Store INCRUSE ELLIPTA at room temperature between 68°F and 77°F (20°C and
529 25°C). Keep in a dry place away from heat and sunlight.
- 530 • Store INCRUSE ELLIPTA in the unopened foil tray and only open when ready for
531 use.
- 532 • Safely throw away INCRUSE ELLIPTA in the trash 6 weeks after you open the foil
533 tray or when the counter reads "0", whichever comes first. Write the date you
534 open the tray on the label on the inhaler.
- 535 • **Keep INCRUSE ELLIPTA and all medicines out of the reach of children.**
536

537 **General information about INCRUSE ELLIPTA**

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

542 This Patient Information leaflet summarizes the most important information about
543 INCRUSE ELLIPTA. If you would like more information, talk with your healthcare
544 provider or pharmacist. You can ask your healthcare provider or pharmacist for
545 information about INCRUSE ELLIPTA that was written for healthcare professionals.

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

548

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

550 Active ingredients: umeclidinium

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

553

554 **Instructions for Use**

555 **For Oral Inhalation Only.**

556

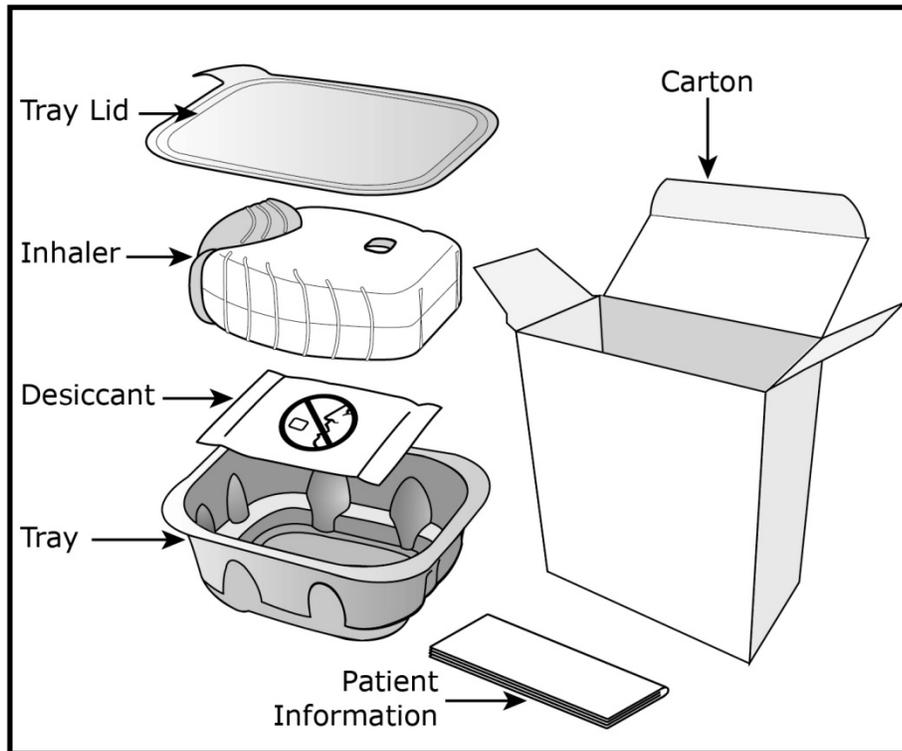
557 **Read this before you start:**

- 558 • **If you open and close the cover without inhaling the medicine, you will**
559 **lose the dose.**
- 560 • **The lost dose will be securely held inside the inhaler, but it will no**
561 **longer be available to be inhaled.**

- 562 • It is not possible to accidentally take a double dose or an extra dose in
563 one inhalation.

564

565 **Your INCRUSE ELLIPTA inhaler**



566

567

568 **How to use your inhaler**

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

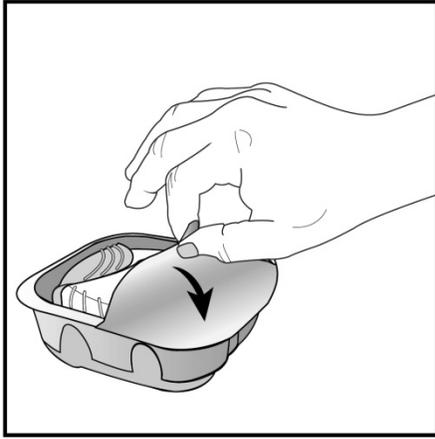


Figure A

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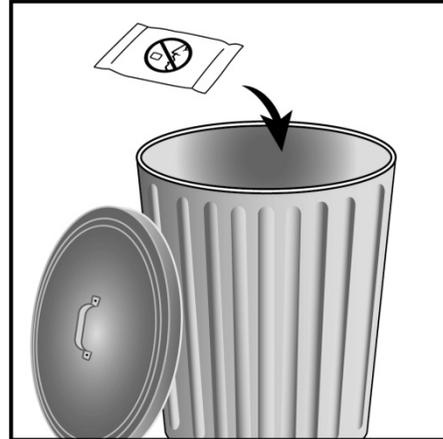


Figure B

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579 **Important Notes:**

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

594
595 **Check the counter. See Figure C.**

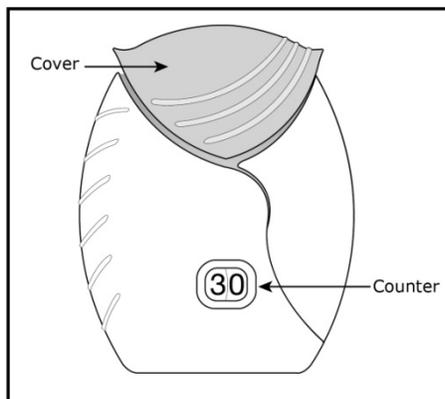


Figure C

- 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.

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Prepare your dose:

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

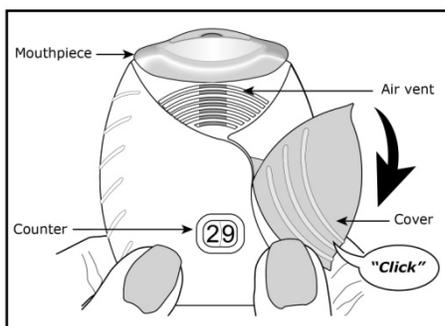


Figure D

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

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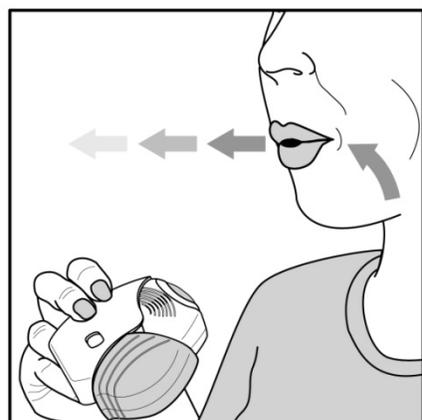


Figure E

- Step 2. Breathe out. See Figure E.**
- While holding the inhaler away from your mouth, breathe out (exhale) fully. Do not breathe out into the mouthpiece.

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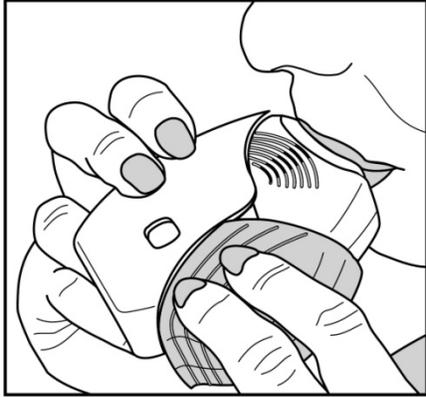


Figure F

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

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

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Do not block the air vent with your fingers.



Figure G

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

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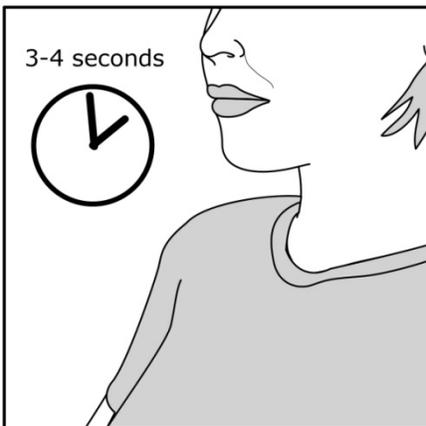


Figure H

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

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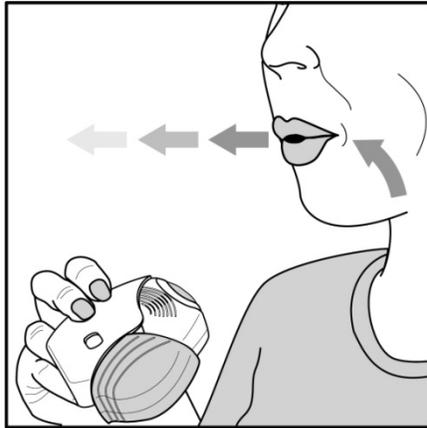


Figure I

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

- 684 • You may not taste or feel the medicine,
 685 even when you are using the inhaler
 686 correctly.
- 687 • **Do not** take another dose from the inhaler
 688 even if you do not feel or taste the
 689 medicine.

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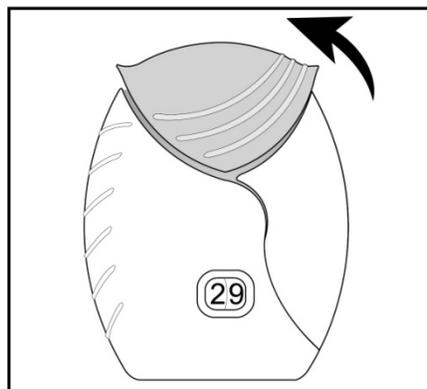


Figure J

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

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

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

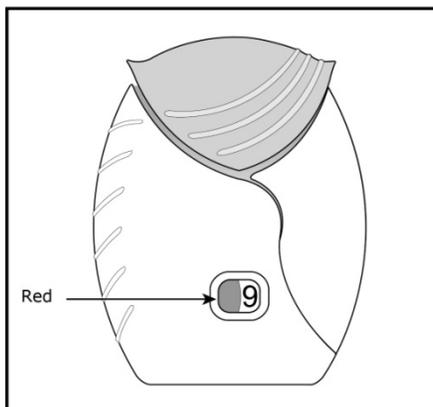


Figure K

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

701
 702

712
 713 If you have questions about INCRUSE ELLIPTA or how to use your inhaler, call
 714 GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.INCRUSE.com.

715

716 **This Patient Information and Instructions for Use have been approved by**
717 **the U.S. Food and Drug Administration.**

718

719 INCRUSE is a trademark and ELLIPTA is a registered trademark of the GSK group of
720 companies.

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723

724 GlaxoSmithKline

725 Research Triangle Park, NC 27709

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728 Month Year

729 INC:xMG