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: 2/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Deterioration of Disease and Acute Episodes

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

INCRUSE ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. INCRUSE ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If INCRUSE ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting $beta_2$-agonist becomes less effective; or the patient needs more short-acting $beta_2$-agonist than usual, these may be markers of deterioration of disease. In this setting a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dose of INCRUSE ELLIPTA beyond the recommended dose is not appropriate in this situation.

5.2 Paradoxical Bronchospasm

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

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

5.3 Hypersensitivity Reactions

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

5.4 Worsening of Narrow-Angle Glaucoma

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

5.5 Worsening of Urinary Retention

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

In the 8 clinical trials conducted to support initial approval of INCRUSE ELLIPTA, a total of 1,663 subjects with COPD (mean age: 62.7 years; 89% white; 65% male across all treatments, including placebo) received at least 1 inhalation dose of umeclidinium at doses of 62.5 or 125 mcg. In the 4 randomized, double-blind, placebo- or active-controlled, efficacy clinical trials, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received the recommended dose of umeclidinium 62.5 mcg. In a 12-month, randomized, double-blind,

placebo-controlled, long-term safety trial, 227 subjects received umeclidinium 125 mcg for up to 52 weeks *[see Clinical Studies (14)]*.

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

Table 1. Adverse Reactions with INCRUSE ELLIPTA with ≥1% Incidence and More Common than 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%

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

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

extrasystoles, sinus tachycardia, idioventricular rhythm, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, and vertigo.

The safety and efficacy of INCRUSE ELLIPTA in combination with an inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) were also evaluated in four 12-week clinical trials. A total of 1,637 subjects with COPD across four 12-week, randomized, double-blind clinical trials received at least 1 dose of INCRUSE ELLIPTA (62.5 mcg) or placebo administered once daily in addition to background ICS/LABA (mean age: 64 years, 88% white, 65% male across all treatments). Two trials (Trials 1 and 2) evaluated INCRUSE ELLIPTA in combination with fluticasone furoate/vilanterol (FF/VI) 100 mcg/25 mcg administered once daily, and 2 trials (Trials 3 and 4) evaluated INCRUSE ELLIPTA administered once daily in combination with fluticasone propionate/salmeterol (FP/SAL) 250 mcg/50 mcg administered twice daily *[see Clinical Studies (14.2)]*. Adverse reactions that occured with INCRUSE ELLIPTA in combination with an ICS/LABA were similar to those reported with INCRUSE ELLIPTA as monotherapy. In addition to the umeclidinium monotherapy adverse reactions reported above, adverse reactions occurring with INCRUSE ELLIPTA in combination with an ICS/LABA, at an incidence of greater than or equal to 1% and exceeding ICS/LABA alone, were oropharyngeal pain and dysgeusia.

7 DRUG INTERACTIONS

7.1 Anticholinergics

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

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

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

Nonteratogenic Effects

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

10 OVERDOSAGE

No case of overdose has been reported with INCRUSE ELLIPTA.

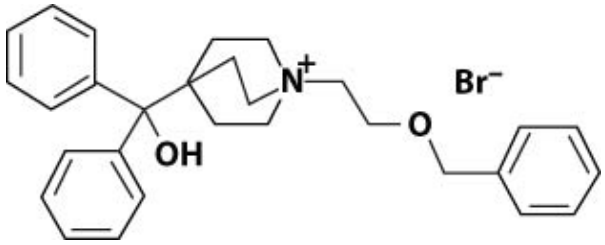
High doses of umeclidinium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a once-daily inhaled dose of up to 1,000 mcg umeclidinium (16 times the maximum recommended daily dose) for 14 days in subjects with COPD.

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

11 DESCRIPTION

INCRUSE ELLIPTA contains the active ingredient umeclidinium, an anticholinergic.

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



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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

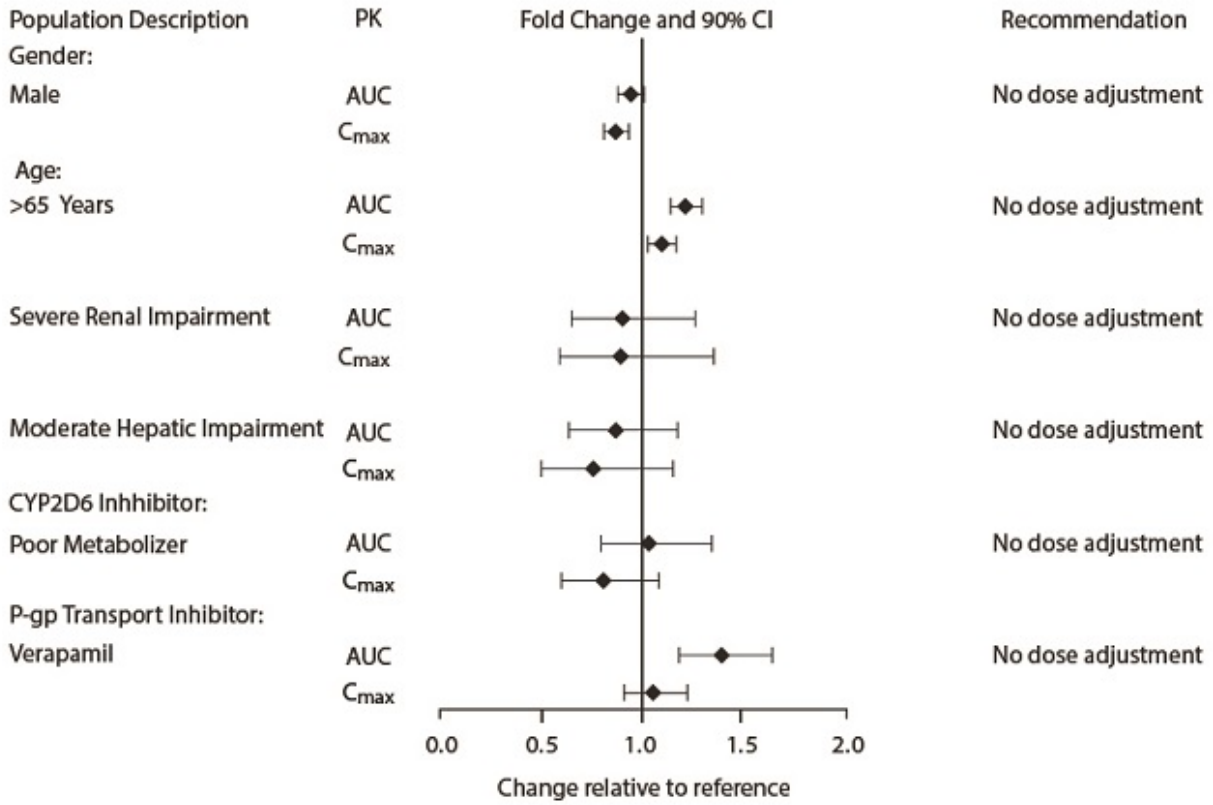
Special Populations

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

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

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

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



Drug Interactions

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Umeclidinium produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 137 and 295/200 mcg/kg/day

(male/female), respectively (approximately 20 and 25/20 times the MRHDID in adults on an AUC basis, respectively).

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

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

14 CLINICAL STUDIES

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

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

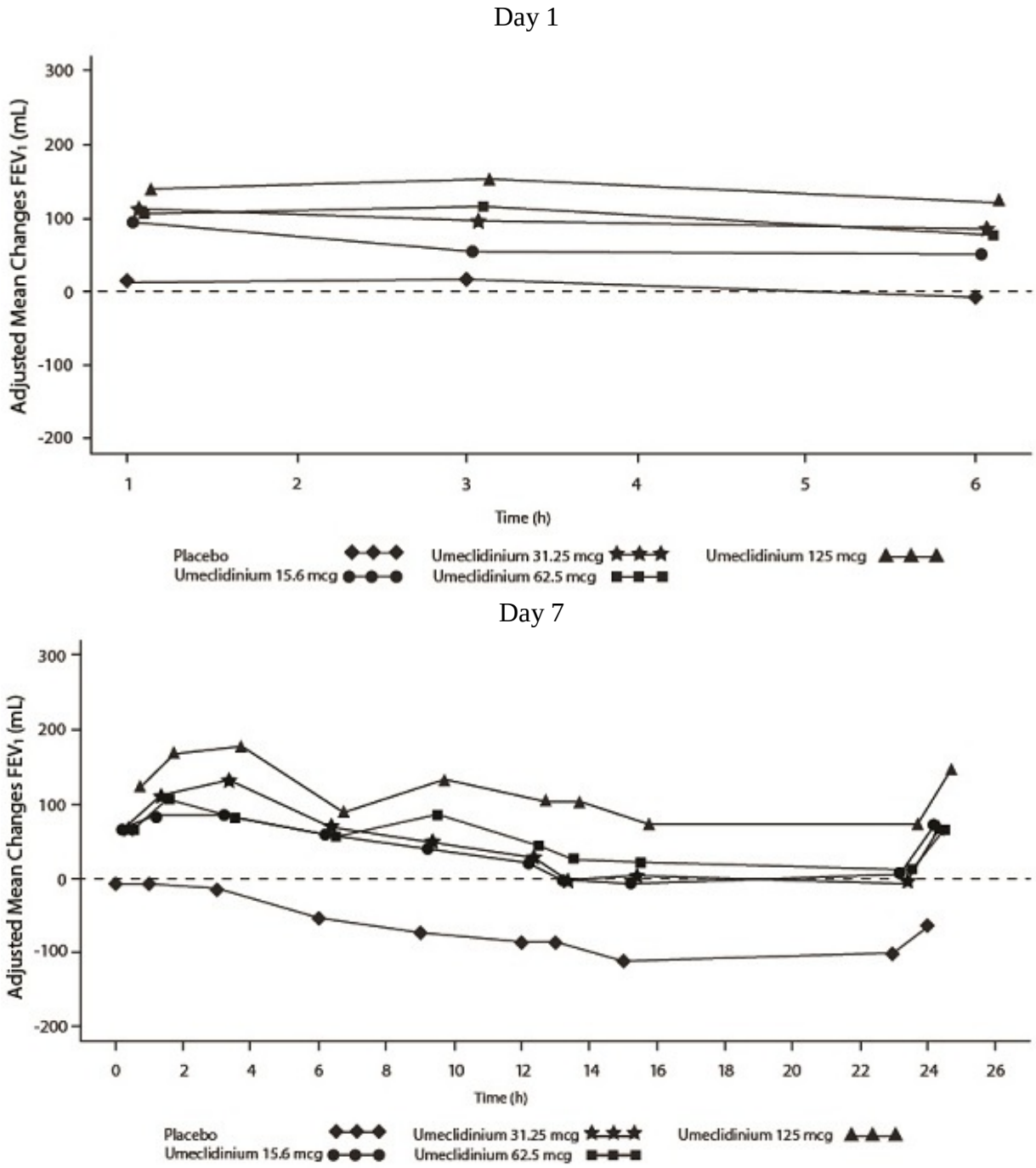
14.1 Dose-Ranging Trials

Dose selection for umeclidinium in COPD was supported by a 7-day, randomized, double-blind, placebo-controlled, crossover trial evaluating 4 doses of umeclidinium (15.6 to 125 mcg) or placebo dosed once daily in the morning in 163 subjects with COPD. A dose ordering was observed, with the 62.5- and 125-mcg doses demonstrating larger improvements in FEV_1 over 24 hours compared with the lower doses of 15.6 and 31.25 mcg (Figure 2).

The differences in trough FEV_1 from baseline after 7 days for placebo and the 15.6-, 31.25-, 62.5-, and 125-mcg doses were -74 mL (95% CI: -118, -31), 38 mL (95% CI: -6, 83), 27 mL (95% CI: -18, 72), 49 mL (95% CI: 6, 93), and 109 mL (95% CI: 65, 152), respectively. Two additional dose-ranging trials in subjects with COPD demonstrated minimal additional benefit at doses above 125 mcg. The dose-ranging results supported the evaluation of 2 doses of umeclidinium, 62.5 and 125 mcg, in the confirmatory COPD trials to further assess dose response.

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

Figure 2. Adjusted Mean Change from Baseline in Postdose Serial FEV_1 (mL) on Days 1 and 7



14.2 Maintenance Treatment: Confirmatory Trials

The clinical development program for INCRUSE ELLIPTA included 2 randomized, double-blind, placebo-controlled, parallel-group trials in subjects with COPD designed to evaluate the efficacy of INCRUSE ELLIPTA on lung function. Trial 1 was a 24-week placebo-controlled

trial, and Trial 2 was a 12-week placebo-controlled trial. These trials treated subjects that had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than or equal to 10 pack-years, had a post-albuterol FEV_1 less than or equal to 70% of predicted normal values, had a ratio of FEV_1/FVC of less than 0.7, and had a Modified Medical Research Council (mMRC) score greater than or equal to 2. Subjects in Trial 1 had a mean age of 63 years and an average smoking history of 46 pack-years, with 50% identified as current smokers. At screening, the mean post-bronchodilator percent predicted FEV_1 was 47% (range: 13% to 74%), the mean post-bronchodilator FEV_1/FVC ratio was 0.47 (range: 0.20 to 0.74), and the mean percent reversibility was 15% (range: -35% to 109%). Baseline demographics and lung function for subjects in Trial 2 were similar to those in Trial 1.

Trial 1 evaluated umeclidinium 62.5 mcg and placebo. The primary endpoint was change from baseline in trough (predose) FEV_1 at Day 169 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours after the previous dose on Day 168) compared with placebo. INCRUSE ELLIPTA 62.5 mcg demonstrated a larger increase in mean change from baseline in trough (predose) FEV_1 relative to placebo (Table 2). Similar results were obtained from Trial 2.

Table 2. Least Squares Mean Change from Baseline in Trough FEV_1 (mL) at Day 169 in the Intent-to-Treat Population (Trial 1)

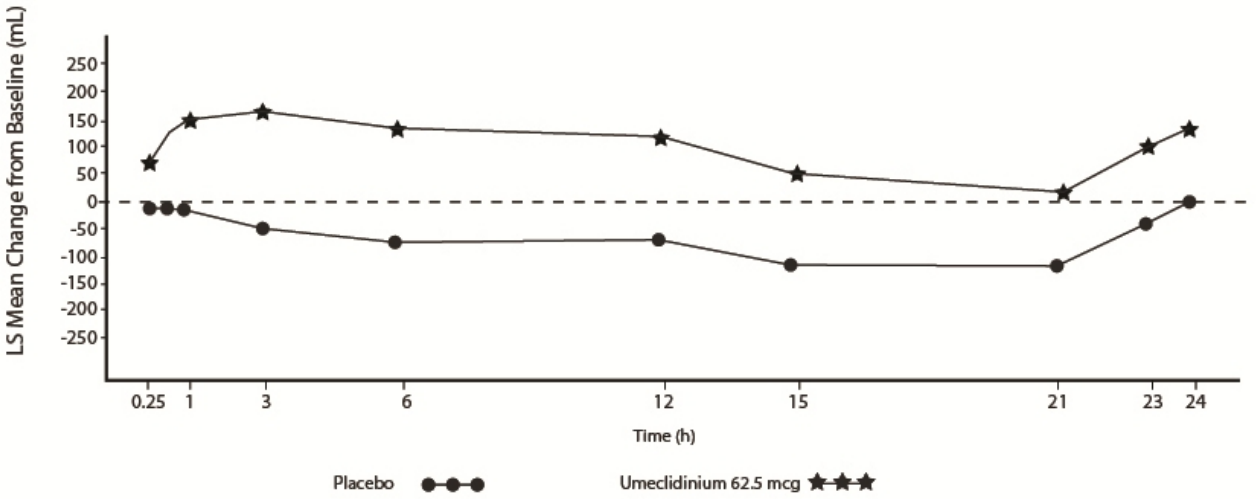
		Trough FEV_1 (mL) at Day 169
		Difference from Placebo (95% CI)
Treatment	**n**	**n = 280**
INCRUSE ELLIPTA	n = 418	115 (76, 155)

n = Number in intent-to-treat population.

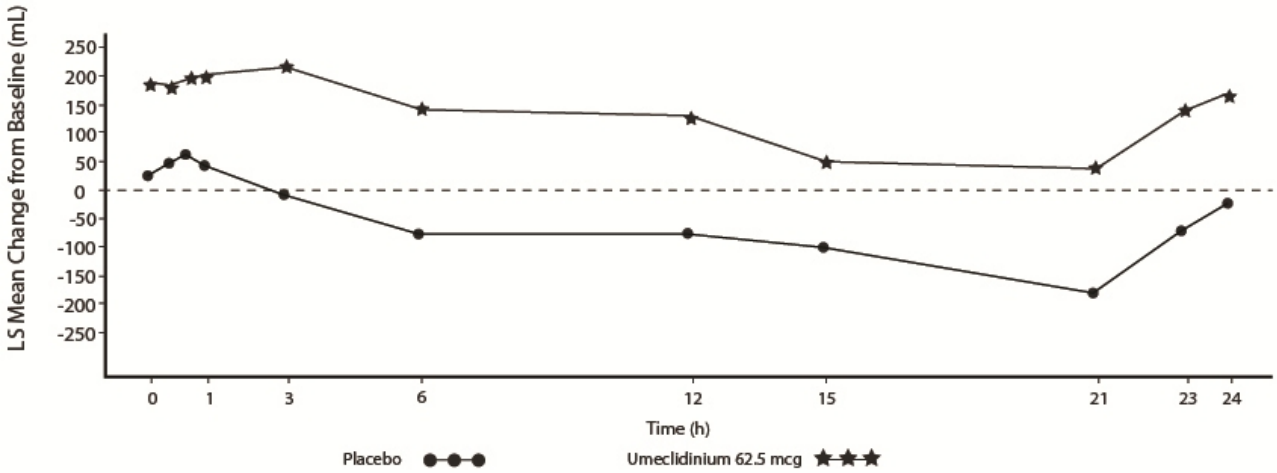
Serial spirometric evaluations throughout the 24-hour dosing interval were performed in a subset of subjects (n = 54, umeclidinium 62.5 mcg; n = 36, placebo) at Days 1, 84, and 168 in Trial 1, and for all patients at Days 1 and 84 in Trial 2. Results from Trial 1 at Day 1 and Day 168 are shown in Figure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

Figure 3. Least Squares (LS) Mean Change from Baseline in FEV_1 (mL) over Time (0-24 h) on Days 1 and 168 (Trial 1 Subset Population)

Day 1



Day 168



In Trial 1, the mean peak FEV_1 (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).

14.3 Maintenance Treatment: Combination with an ICS/LABA Trials

The efficacy of INCRUSE ELLIPTA in combination with an ICS/LABA was evaluated in 4 randomized, double-blind, parallel-group trials in subjects with COPD. These trials, all of similar study design, were of 12-weeks' treatment duration. Subjects were randomized to INCRUSE ELLIPTA 62.5 mcg + ICS/LABA or placebo + ICS/LABA. Entry criteria for subjects enrolled in these trials were similar to those described above in Section 14.2. The primary endpoint for these trials was change from baseline in trough (predose) FEV_1 at Day 85 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours after the previous dose on Day 84). Baseline FEV_1 was measured while subjects were on background ICS/LABA.

Combination with Fluticasone Furoate + Vilanterol

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

Subjects in Trial 1 across all treatment arms had a mean age of 64 years and an average smoking history of 50 pack-years, with 42% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 13% to 76%), the mean postbronchodilator FEV_1/FVC ratio was 0.48 (range: 0.22 to 0.70), and the mean percent reversibility was 14% (range: -20% to 71%).

The primary endpoint was change from baseline in trough (predose) FEV_1 at Day 85 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours after the previous dose on Day 84) compared with placebo (INCRUSE ELLIPTA + FF/VI vs. placebo + FF/VI). INCRUSE ELLIPTA + FF/VI demonstrated a larger mean change from baseline in trough (predose) FEV_1 relative to placebo + FF/VI (Table 3).

Table 3. Least Squares Mean Change from Baseline in Trough FEV_1 (mL) at Day 85 in the Intent-to-Treat Population (Trial 1)

		Trough FEV_1 (mL) at Day 85
		Difference from Placebo + FF/VI (95% CI)
Treatment	**n**	**n = 206**
INCRUSE ELLIPTA + FF/VI	n = 206	124 (93, 154)

FF/VI = Fluticasone furoate/vilanterol.
n = Number in intent-to-treat population.

Combination with Fluticasone Propionate + Salmeterol

Trials 3 and 4 randomized subjects to INCRUSE ELLIPTA 62.5 mcg + FP/SAL 250 mcg/50 mcg or placebo + FP/SAL 250 mcg/50 mcg. The treatments with INCRUSE

ELLIPTA and placebo were administered once daily, while the FP/SAL treatment was administered twice daily. Trial population demographics and results for Trials 3 and 4 were similar; therefore, only Trial 3 results are presented below.

Subjects in Trial 3 across all treatment arms had a mean age of 63 years and an average smoking history of 50 pack-years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 47% (range: 12% to 70%), the mean postbronchodilator FEV_1/FVC ratio was 0.47 (range: 0.22 to 0.69), and the mean percent reversibility was 16% (range: -36% to 79%).

The primary endpoint was change from baseline in trough (predose) FEV_1 at Day 85 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours after the previous dose on Day 84) compared with placebo (INCRUSE ELLIPTA + FP/SAL vs. placebo + FP/SAL). INCRUSE ELLIPTA + FP/SAL demonstrated a larger mean change from baseline in trough (predose) FEV_1 relative to placebo + FP/SAL (Table 4).

Table 4. Least Squares Mean Change from Baseline in Trough FEV_1 (mL) at Day 85 in the Intent-to-Treat Population (Trial 3)

		Trough FEV_1 (mL) at Day 85
		Difference from Placebo + FP/SAL (95% CI)
Treatment	**n**	**n = 205**
INCRUSE ELLIPTA+FP/SAL	n = 204	147 (107, 187)

FP/SAL = Fluticasone propionate/salmeterol.
n = Number in intent-to-treat population.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

Not for Acute Symptoms

Inform patients that INCRUSE ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medicine and instruct them in how it should be used.

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

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

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

Paradoxical Bronchospasm

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

Worsening of Narrow-Angle Glaucoma

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

Worsening of Urinary Retention

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

GlaxoSmithKline
Research Triangle Park, NC 27709

INC:xPI

Patient Information

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

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

Who should not use INCRUSE ELLIPTA?

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 “What are the ingredients in INCRUSE ELLIPTA?” below for a complete list of ingredients.

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

Tell your healthcare provider about all of your health 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.
- have any other medical conditions.

- are pregnant or planning 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 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 unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **INCRUSE ELLIPTA does not relieve sudden breathing problems.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:

- your breathing problems get worse.
- you need to use your rescue inhaler more often than usual.
- your rescue inhaler does not work as well to relieve your symptoms.

What are the possible side effects with 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.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
- **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 infection
- stuffy or runny nose
- cough
- sore throat

- joint pain
- muscle pain
- tooth pain
- stomach pain
- bruising or dark areas of skin
- fast or irregular heartbeat

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

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

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

How do I store 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 not mentioned in a Patient Information leaflet. Do not use INCRUSE ELLIPTA for a condition for which it was not prescribed. Do not give your INCRUSE ELLIPTA to other people, even if they have the same condition that you have. It may harm them.

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

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

What are the ingredients in INCRUSE ELLIPTA?

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

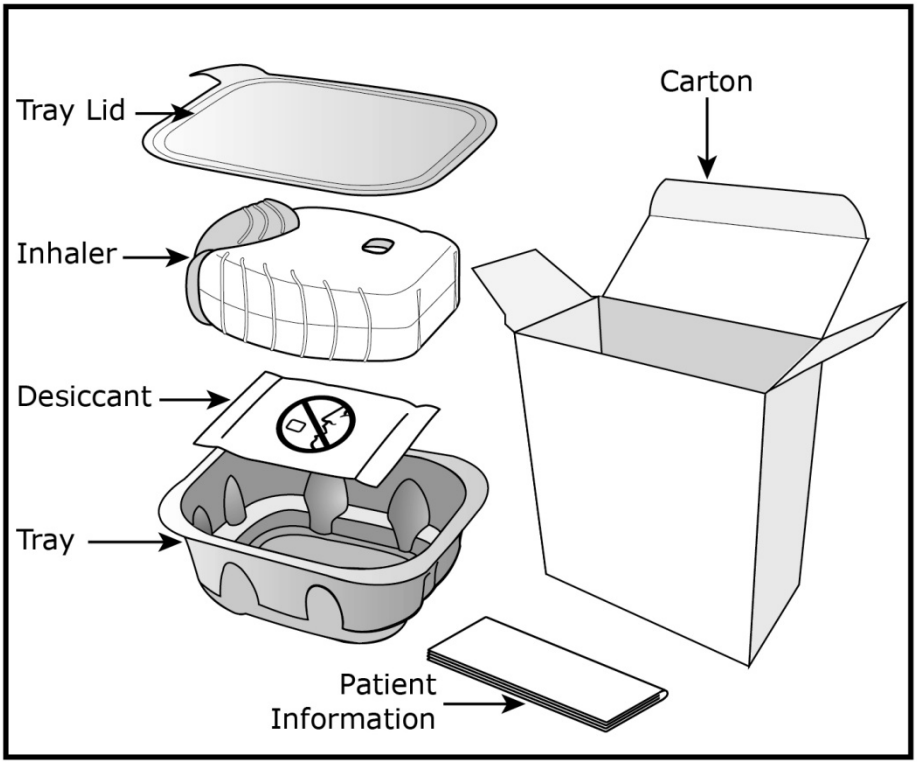
Instructions for Use

For Oral Inhalation Only.

Read this before you start:

- **If you open and close the cover without inhaling the medicine, you will lose the dose.**
- **The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.**
- **It is not possible to accidentally take a double dose or an extra dose in 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 inhale. Throw it away in the household trash out of reach of children and pets. See Figure B.

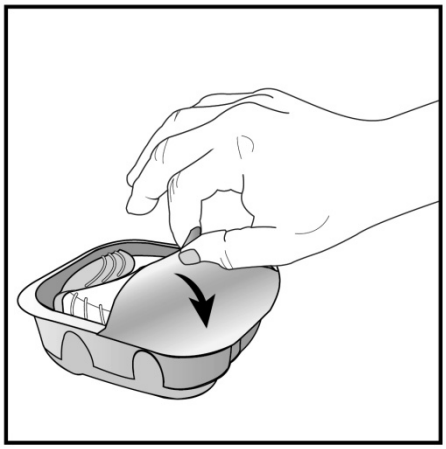


Figure A

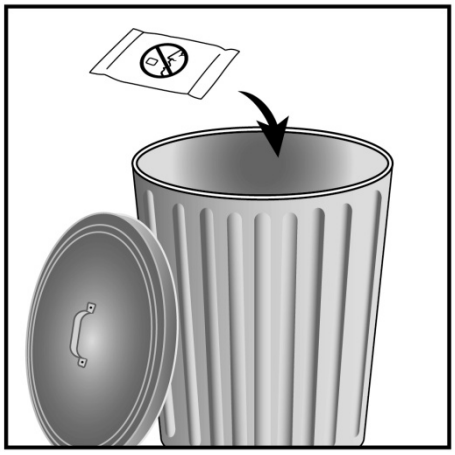


Figure B

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.

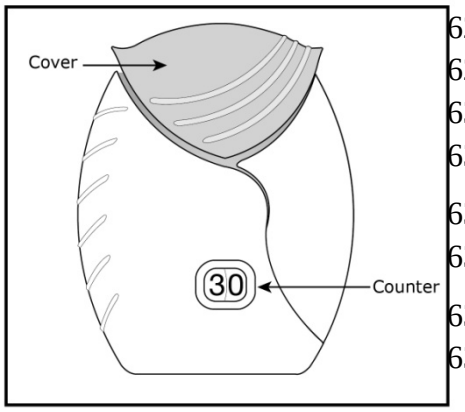


Figure C

- 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.

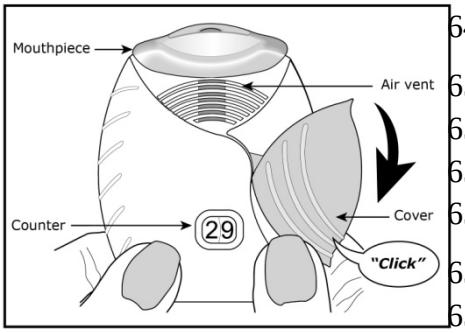


Figure D

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

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

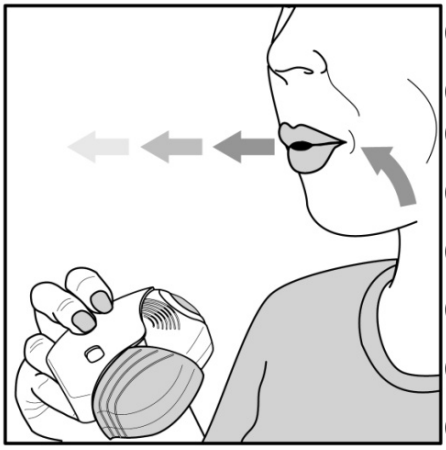


Figure E

Step 2. Breathe out. See Figure E.

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

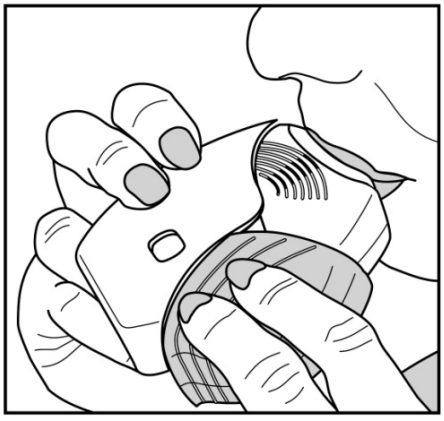


Figure F

Step 3. Inhale your medicine. See Figure F.

- Put the mouthpiece between your lips, and close your lips firmly around it. Your lips should fit over the curved shape of the mouthpiece.
- Take 1 long, steady, deep breath in through your mouth. **Do not** breathe in through your nose.

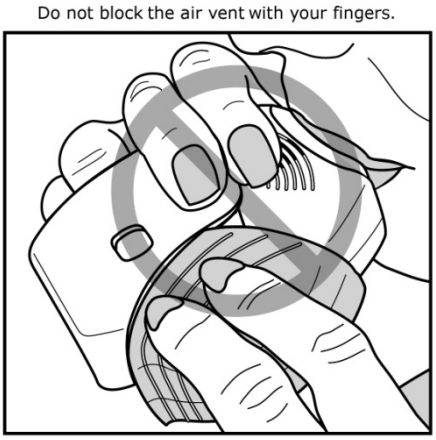


Figure G

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

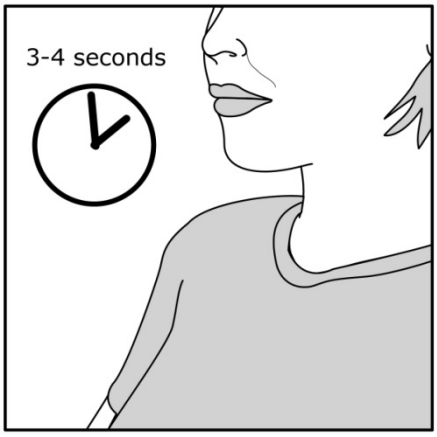


Figure H

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

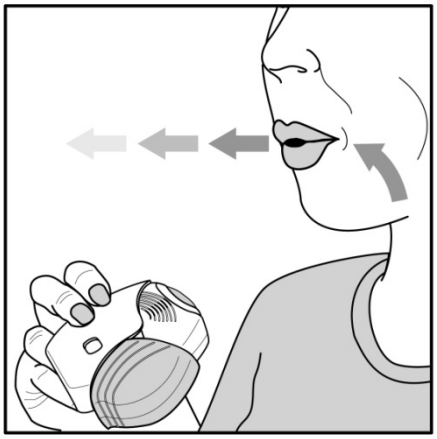


Figure I

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

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

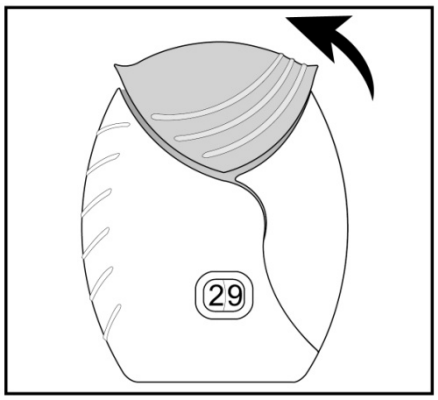


Figure J

Step 5. Close the inhaler. See Figure J.

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

Important Note: When should you get a refill?

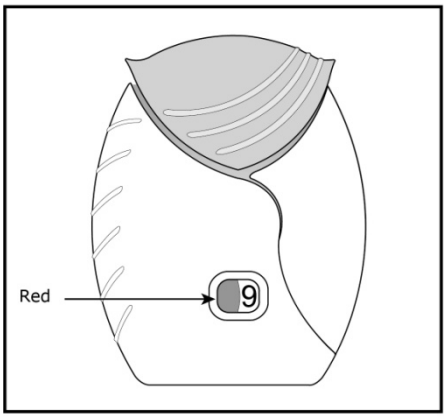


Figure K

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

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

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

GlaxoSmithKline
Research Triangle Park, NC 27709

748
749 Month Year
750 INC:xPIL