PRODUCT MONOGRAPH

[Pr]INCRUSE ELLIPTA

umeclidinium (as bromide) dry powder for oral inhalation

62.5 mcg umeclidinium per oral inhalation

Inhaled Bronchodilator

Long-Acting Muscarinic Antagonist (LAMA)

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TABLE OF CONTENTS

PAGE

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umeclidinium (as bromide) dry powder for oral inhalation

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral Inhalation	Dry powder for oral inhalation / 62.5 mcg umeclidinium (as bromide)	Lactose monohydrate (which contains milk protein) and magnesium stearate

INDICATIONS AND CLINICAL USE

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

INCRUSE ELLIPTA is **not** indicated for the relief of acute deterioration of COPD.

Geriatrics:

No dosage adjustment is required in patients over 65 years of age.

Pediatrics:

INCRUSE ELLIPTA should not be used in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to umeclidinium or any ingredient in the formulation or component of the container (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with severe hypersensitivity to milk proteins.

WARNINGS AND PRECAUTIONS

General

Acute bronchospasm
INCRUSE ELLIPTA is not indicated for the treatment of acute episodes of bronchospasm, i.e., as rescue therapy. INCRUSE ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD. The initiation of INCRUSE ELLIPTA in this setting is not appropriate. An inhaled, short-acting bronchodilator, should be used to relieve acute symptoms such as shortness of breath. When prescribing INCRUSE ELLIPTA, the physician must also provide the patient with an inhaled, short-acting bronchodilator for treatment of acute symptoms. Patients should be advised to have their short-acting bronchodilator available at all times.

When beginning treatment with INCRUSE ELLIPTA patients who have been taking oral or inhaled, short-acting bronchodilators on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

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

Exacerbations may occur during treatment with INCRUSE ELLIPTA. Patients should be advised to continue treatment and seek medical advice if COPD symptoms remain uncontrolled or worsen after initiation of therapy with INCRUSE ELLIPTA.

Excessive Use
As with other inhaled bronchodilators, INCRUSE ELLIPTA should not be used more often or at higher doses than recommended.

INCRUSE ELLIPTA should not be administered concomitantly with other medicines containing a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium), as an overdose may result.

There have been no studies to investigate the effect of INCRUSE ELLIPTA on the ability to perform tasks that require judgement, motor or cognitive skills. The occurrence of headache or blurred vision may influence the ability to drive or to use machinery.

Anticholinergic Effects
Consistent with its antimuscarinic activity, INCRUSE ELLIPTA should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Worsening of Narrow-Angle Glaucoma
INCRUSE ELLIPTA, like other antimuscarinic-containing products, 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 coloured images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

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

Carcinogenesis and Mutagenesis

Animal data only (see TOXICOLOGY section).

Cardiovascular

Cardiovascular effects, such as cardiac arrhythmias, e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists, including INCRUSE ELLIPTA. Therefore, INCRUSE ELLIPTA should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias. In some cases, treatment may need to be discontinued (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

Respiratory

Paradoxical bronchospasm
As with other inhalation therapies, administration of INCRUSE ELLIPTA may produce paradoxical bronchospasm that may be life-threatening. Treatment with INCRUSE ELLIPTA should be discontinued if paradoxical bronchospasm occurs and alternative therapy considered if necessary.

Ophthalmologic

Worsening of Narrow-Angle Glaucoma (see Anticholinergic Effects).

Hypersensitivity

Immediate Hypersensitivity Reactions

As with all medications, immediate hypersensitivity reactions may occur after administration of INCRUSE ELLIPTA. If signs suggesting allergic reactions (in particular, difficulties in breathing or swallowing, swelling of tongue, lips and face, urticaria, skin rash) occur, INCRUSE ELLIPTA should be discontinued immediately and alternative therapy instituted. The patient should NOT be re-challenged with INCRUSE ELLIPTA (see CONTRAINDICATIONS).

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 take INCRUSE ELLIPTA (see CONTRAINDICATIONS).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies with INCRUSE ELLIPTA in pregnant women. INCRUSE ELLIPTA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus. Women should be advised to contact their physician if they become pregnant while taking INCRUSE ELLIPTA.

Labour and Delivery: There are no adequate and well-controlled human studies that have investigated the effects of umeclidinium during labour and delivery. INCRUSE ELLIPTA should be used during labour only if the potential benefit justifies the potential risk.

Nursing Women: It is unknown whether umeclidinium is excreted in human breast milk. However, other muscarinic antagonists (including metabolites) are excreted into the milk of lactating rats. A risk to breastfed newborns/infants cannot be excluded. Therefore, the use of INCRUSE ELLIPTA by breast-feeding women should only be considered if the expected benefit to the woman is greater than any possible risk to the infant.

Pediatrics: INCRUSE ELLIPTA is not indicated for use in children and therefore should not be used in patients under 18 years of age.

Geriatrics: Four well-controlled (12-week and 24-week) studies with INCRUSE ELLIPTA 62.5 mcg or umeclidinium 125 mcg included 810 subjects aged 65 years and older, and of those, 183 subjects were aged 75 years and older. No overall differences in safety were observed between these subjects and younger subjects, but greater sensitivity in some older individuals cannot be ruled out.

Hepatic Impairment: Subjects with moderate hepatic impairment (Child-Pugh score of 7-9) showed no relevant increase in systemic exposure to umeclidinium (C_{max} and AUC), and no relevant difference in protein binding between subjects with moderate hepatic impairment and healthy volunteers. INCRUSE ELLIPTA has not been evaluated in subjects with severe hepatic impairment.

Renal Impairment: Subjects with severe renal impairment (CrCl <30 mL/min) showed no relevant increase in systemic exposure to umeclidinium (C_{max} and AUC), and no relevant difference in protein binding between subjects with severe renal impairment and healthy volunteers.

Monitoring and Laboratory Tests

Not applicable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

INCRUSE ELLIPTA contains a long-acting muscarinic antagonist. Adverse reactions to INCRUSE ELLIPTA are expected to be similar in nature to other muscarinic antagonists. Adverse reactions that have been associated with other muscarinic antagonists include cardiovascular effects (atrial arrhythmias and tachycardia), ocular disorders (blurred vision), urinary retention, gastrointestinal disorders, dry mouth and cough.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The safety profile of INCRUSE ELLIPTA is primarily based on 1,663 subjects with COPD across 8 clinical studies who received at least one inhalation dose of INCRUSE ELLIPTA 62.5 mcg or umeclidinium 125 mcg (mean age 62.7, 89% white, 65% male; across all treatment arms, including placebo). In the four pivotal randomized, double-blind, placebo or active comparator-controlled efficacy clinical studies, 1,185 subjects received umeclidinium for up to 24 weeks, of which 487 subjects received the recommended dose of INCRUSE ELLIPTA 62.5 mcg. In a randomized, double-blind, placebo-controlled long-term safety study, 227 subjects received umeclidinium 125 mcg for up to 52 weeks. Patients were excluded from clinical studies if they had clinically significant cardiovascular abnormalities that were uncontrolled or a significant ECG finding from the 12-lead ECG conducted at the study entry.

12-week and 24-week pivotal studies

The incidence of adverse events presented in Table 1 is based upon two pivotal placebo-controlled efficacy studies: one 12-week study and one 24-week study. Adverse events in subjects receiving INCRUSE ELLIPTA reported with a frequency of equal to or greater than 1%, and exceeding the rate in subjects receiving placebo are listed in Table 1.

Table 1 Adverse Events With INCRUSE ELLIPTA With ≥1% Incidence and More Common Than with Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Event	INCRUSE ELLIPTA 62.5 mcg (n=487) %	Placebo (n=348) %
Infections and Infestations		
Nasopharyngitis	8	7
Upper respiratory tract infection	5	4
Viral upper respiratory tract infection	1	<1
Pharyngitis	1	<1
Respiratory, thoracic, and mediastinal disorders		
Cough	3	2
Injury, poisoning and procedural complications		
Contusion	1	<1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	2	1
Myalgia	1	<1
Gastrointestinal disorders		
Abdominal pain upper	1	<1
Toothache	1	<1
Cardiac disorders		
Tachycardia	1	<1

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cardiac disorders: atrial fibrillation.
Gastrointestinal disorders: constipation.
Infections and Infestations: sinusitis.

52-week study
In a long-term safety study, 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 study were similar to those of the efficacy studies. Patients with an abnormal/significant ECG finding or from 24-hour Holter monitoring finding during the study withdrew from the study.

The adverse events reported in subjects receiving umeclidinium 125 mcg with a frequency of equal to or greater than 1% and exceeding the rate in subjects receiving placebo in this study were: upper respiratory tract infection, pharyngitis, pneumonia, lower respiratory tract infection, rhinitis, headache, dizziness, sinus headache, cough, back pain, arthralgia, pain in extremity, neck pain, myalgia, nausea, dyspepsia, diarrhea, rash, depression, vertigo, nasopharyngitis, supraventricular extrasystoles, sinus tachycardia, supraventricular tachycardia, rhythm idioventricular, and urinary tract infection.

12-week additional studies
The safety of INCRUSE ELLIPTA in combination with an inhaled corticosteroid/long-acting $beta_2$-adrenergic agonist (ICS/LABA) was evaluated in four 12-week clinical trials. A total of 1,640 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) (see DETAILED PHARMACOLOGY, Clinical Pharmacology). Two trials evaluated INCRUSE ELLIPTA in combination with fluticasone furoate/vilanterol (FF/VI) 100 mcg/25 mcg administered once daily; and 2 trials evaluated INCRUSE ELLIPTA administered once daily in combination with fluticasone propionate/salmeterol (FP/SAL) 250 mcg/50 mcg administered twice daily. Adverse reaction profiles seen in these four 12-week studies were similar to that observed in pivotal studies and the 52-week long-term study. 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.

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified from post-approval use of INCRUSE ELLIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders: dysgeusia (common)

Immune System Disorders: hypersensitivity reactions including: rash, urticaria and pruritus (uncommon); anaphylaxis (rare), angioedema (rare)

Eye Disorders: vision blurred (unknown), eye pain (unknown), glaucoma (unknown)

Renal and Urinary Disorders: urinary retention (unknown), dysuria (unknown)

DRUG INTERACTIONS

Drug-Drug Interactions

Metabolic and transporter based drug interactions
Umeclidinium is a substrate of cytochrome P450 2D6 (CYP2D6); however umeclidinium pharmacokinetics were not significantly affected in a population of CYP2D6 poor metabolizers (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Umeclidinium is a substrate of P-glycoprotein (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 volunteers. An approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on C_{max}. A decrease in blood potassium, an increase in QTc interval and an increased number of supraventricular tachycardia events occurred with co-administration with verapamil (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Clinically significant interactions mediated by umeclidinium at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Table 2 Established or Potential Drug-Drug Interactions

Drug Class	Ref	Effect	Clinical comment
Anticholinergics	T	There is potential for an interaction with concomitantly used anticholinergic medications.	Avoid co-administration with other anticholinergic-containing drugs.
Inhibitors of P-gp	CT	May alter the systemic exposure to umeclidinium resulting in pharmacodynamics effects.	An approximately 1.4-fold increase in umeclidinium AUC was observed. No effect of verapamil was observed on umeclidinium C_{max}. No dose adjustment is warranted.
CYP2D6 inhibitors	T	May alter systemic exposure to umeclidinium resulting in pharmacodynamics effects.	Umeclidinium pharmacokinetics were not significantly affected in a population of CYP2D6 poor metabolizers. No dose adjustment is warranted.

Abbreviations: CT=Clinical Trial; T=Theoretical

Drug-Food Interactions

Interactions with food have not been evaluated. The oral bioavailability of umeclidinium is <1%, therefore no food effect study was performed.

Drug-Herb Interactions

Interactions with herbal products have not been evaluated.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been evaluated.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Counselling by doctors on smoking cessation should be the first step in treating patients with COPD who smoke, independent of the clinical presentation i.e. chronic bronchitis (with or without airflow limitation) or emphysema. Cessation of smoking produces dramatic symptomatic benefits and has been shown to confer a survival advantage.
- INCRUSE ELLIPTA should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing a long-acting muscarinic antagonist, as an overdose may result.

- When beginning treatment with INCRUSE ELLIPTA, patients who have been taking oral or inhaled, short-acting bronchodilators on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms.

- Patients should be made aware that for optimum benefit, INCRUSE ELLIPTA must be used regularly, even when asymptomatic.

Recommended Dose and Dosage Adjustment

The recommended dose is one inhalation of INCRUSE ELLIPTA 62.5 mcg once daily.

Dosing in Special Populations

No dosage adjustment is required in patients over 65 years of age, in patients with renal impairment, or in patients with mild or moderate hepatic impairment. INCRUSE ELLIPTA has not been studied in patients with severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

INCRUSE ELLIPTA should not be used in patients under 18 years of age.

Missed Dose

If a dose is missed, the patient should be instructed to take the next dose when it is due. The patient should not be instructed to take an extra dose.

Administration

INCRUSE ELLIPTA is for oral inhalation only.

INCRUSE ELLIPTA should be administered once-daily at the same time of the day each day.

OVERDOSAGE

No data from clinical studies are available regarding overdose with INCRUSE ELLIPTA.

An overdose of INCRUSE ELLIPTA will likely produce signs and symptoms consistent with the known inhaled muscarinic antagonist adverse effects (e.g., dry mouth, visual accommodation disturbances and tachycardia).

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.

If overdose occurs, discontinue INCRUSE ELLIPTA and initiate appropriate symptomatic and/or supportive therapy.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

INCRUSE ELLIPTA is a once-daily inhaled long-acting muscarinic receptor antagonist (LAMA), also referred to as a long-acting anticholinergic. It is a quinuclidine derivative that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Following oral inhalation, it acts locally on airways to produce bronchodilation. Umeclidinium exerts its 24-hour bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic acetylcholine receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Pharmacodynamics

Cardiac Electrocardiography

The effect of umeclidinium 500 mcg (8X therapeutic dose) on the ECG parameters was investigated in 103 healthy subjects in a double-blind, randomized, placebo- and active-controlled, incomplete block, crossover study. Following repeat doses of umeclidinium 500 mcg once daily for 10 days, no clinically relevant effect on prolongation of QTcF interval ($QTcF=QT/RR^{0.33}$) was observed. UMEC 500 mcg was associated with small positive mean differences from placebo in heart rate from 4 to 24 h, inclusive, with a maximum mean difference of 2.1 bpm (90% CI: 0.7, 3.5) at 8 h.

Pharmacokinetics

Table 3 Summary of Umeclidinium Pharmacokinetic Parameters in Healthy Subjects

	T_{max} (h) Median (range)	$t_{½}$ (h) Geometric Mean (CV%)
Umeclidinium 500 mcg	0.1 (0.08, 0.23)	25.9 (0.1)

Table 4 Summary of Umeclidinium (C_{max} and $AUC_{(0-24)}$) in Subjects with COPD (Geometric Mean [95% CI])

INCRUSE ELLIPTA 62.5 mcg	C_{max} (pg/mL)	$AUC_{(0-24)}$ (pg.h/mL)
Umeclidinium 62.5 mcg[1]	70 (67, 74)	318 (303, 334)

[1]Population pharmacokinetic analyses across 2 trials in subjects with COPD who received INCRUSE ELLIPTA (DB2116975).

Absorption: Following inhaled administration of umeclidinium in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled umeclidinium was on average 13% of the dose, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium, steady state was achieved within 7 to 10 days with 1.5 to 2-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* studies showed that umeclidinium is metabolized principally by the cytochrome P450 enzyme CYP2D6 and is a substrate for the P-gp transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (e.g., glucuronidation, etc), 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.

Excretion: Plasma clearance following intravenous administration was 151 L/hour. Following intravenous administration, approximately 58% of the administered radio-labelled dose (or 73% of the recovered radioactivity) was excreted in feces and 22% of the administered radio-labelled dose (27% of recovered radioactivity) in urine. The excretion of the drug-related material in the feces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male subjects, total radioactivity was excreted primarily in feces (92% of the administered radio-labelled dose). Less than 1% of the orally administered dose was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium plasma elimination

half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% drug excreted unchanged in urine at steady-state.

Special Populations and Conditions

Geriatrics: A population pharmacokinetic analysis showed that pharmacokinetics of umeclidinium are similar between COPD patients 65 years and older and those younger than 65 years of age.

Gender: A population pharmacokinetic analysis showed that no dose adjustment is required for umeclidinium based on the effect of gender.

Race: A population pharmacokinetic analysis showed that no dose adjustment is required for umeclidinium based on the effect of race.

Hepatic Impairment: The pharmacokinetics of umeclidinium have 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), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium has not been evaluated in subjects with severe hepatic impairment.

Renal Impairment: The pharmacokinetics of umeclidinium have been evaluated in subjects with severe renal impairment (creatinine clearance < 30 mL/min). Umeclidinium systemic exposure was not significantly increased (10% for AUC), and there was no evidence of altered protein binding between subjects with severe renal impairment and healthy volunteers.

STORAGE AND STABILITY

Do not store above 30°C. Store in a dry place away from direct heat or sunlight.

Keep out of sight and reach of children.

SPECIAL HANDLING INSTRUCTIONS

INCRUSE ELLIPTA is provided in a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid, which together provide moisture protection, and should only be opened when it is ready to be used for the first time. Once the tray is opened, the desiccant package should be discarded.

Patients should be instructed to write the date the inhaler should be discarded on the label in the space provided. The date should be added as soon as the inhaler has been removed from the tray.

INCRUSE ELLIPTA should be safely discarded when the dose counter reads “0” or 6 weeks after it was removed from the foil tray, whichever comes first.

DOSAGE FORMS, COMPOSITION AND PACKAGING

INCRUSE ELLIPTA is supplied as a disposable grey and light green plastic inhaler containing a foil 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).

Non-medicinal ingredients: lactose monohydrate and magnesium stearate. The lactose monohydrate contains milk proteins.

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

INCRUSE ELLIPTA is supplied with either 30 or 7 blisters on each strip.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

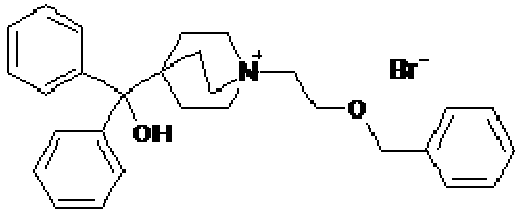
Drug Substance

Proper name: umeclidinium bromide

Chemical name: 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide

Molecular formula and molecular mass: $C_{29}H_{34}NO_2 \bullet Br$ 508.5

Structural formula:



Physicochemical properties: umeclidinium bromide is a white powder. It is slightly soluble in water.

CLINICAL TRIALS

Study Design

The efficacy and safety of INCRUSE ELLIPTA (umeclidinium 62.5 mcg once daily) was evaluated in two pivotal randomized, double-blind, parallel-group, placebo-controlled clinical studies in adult subjects with COPD associated with chronic bronchitis and/or emphysema; a 12-week study (AC4115408) and a 24-week study (DB2113373).

AC4115408 was a 12-week placebo-controlled study, and DB2113373 was a 24-week placebo-controlled study. Both trials had similar inclusion/exclusion criteria and concomitant medications. For AC4115408, the primary efficacy endpoint was trough FEV_1 at Day 85 (Week 12), and the secondary efficacy endpoints were weighted mean FEV_1 over 0-6 hours at Day 1 and at Weeks 4 and 12 and serial FEV_1 at Day 1 and Week 12. For DB2113373, the primary efficacy endpoint was trough FEV_1 at Day 169 (Week 24), and the secondary efficacy endpoint was weighted mean FEV_1 over 0-6 hours at Day 168 (Week 24). Transitional Dyspnea Index (TDI) focal score, St. George's Respiratory Questionnaire (SGRQ) and daily rescue medication use were assessed as other efficacy endpoints in these trials.

Table 5 Summary of Trial Design and Patient Demographics for Clinical Trials

Study #	Trial design, route of administration and study duration	Treatment and Dosage	Study Subjects Mean age (Range) Gender (%)	Primary Efficacy Endpoint
AC4115408	12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of INCRUSE ELLIPTA Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease	INCRUSE ELLIPTA (UMEC 62.5 mcg) UMEC 125 mcg Placebo	Total: 206 63 years (41-86) Male: 62% Female: 38%	Trough FEV_1 at Day 85
DB2113373	24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of ANORO ELLIPTA inhalation powder and the individual components delivered once-daily via a novel dry powder inhaler in subjects with COPD	INCRUSE ELLIPTA (UMEC 62.5 mcg) ANORO ELLIPTA (UMEC/VI 62.5/25 mcg) VI 25 mcg Placebo	Total: 1532 63 years (40-93) Male: 71% Female: 29%	Trough FEV_1 at Day 169

Abbreviations: UMEC = umeclidinium, VI = vilanterol

Patient Demographics and Baseline Characteristics

A total of 1,738 subjects were randomized and received treatments from pivotal studies AC4115408 and DB2113373 (Table 5). The subjects had a clinical diagnosis of COPD,

were 40 years of age or older, had a history of smoking equal to or greater than 10 pack-years, had moderate-to-very severe airflow obstruction (a post-salbutamol $FEV_1 \leq 70\%$ of predicted normal values, and a ratio of $FEV_1/FVC < 0.7$), and dyspnea (a Modified Medical Research Council (mMRC) score ≥ 2). Concurrent use of systemic corticosteroids, long-acting bronchodilators, including theophyllines, was not allowed and previous use of umeclidinium was not allowed. Concurrent use of inhaled corticosteroids (ICS) at a stable dose and study-provided rescue salbutamol were allowed. Subjects with a current diagnosis of asthma, α 1-antitrypsin deficiency, any clinically significant uncontrolled disease, a clinically significant ECG or clinically significant laboratory finding, or a lower respiratory tract infection or recent COPD exacerbation were excluded.

The majority of the 904 patients receiving umeclidinium or placebo in the AC4115408 and DB2113373 trials were male (69%), white (85%), with a mean age of 63.3 years. At baseline, the mean post-bronchodilator FEV_1 was 1355 mL (GOLD II [45%], GOLD III [43%], GOLD IV [13%]). Mean $beta_2$-agonist responsiveness was 13.5% of baseline (137 mL).

Study Results

Lung Function

The pivotal placebo-controlled study (AC4115408) evaluated the efficacy of INCRUSE ELLIPTA compared with placebo, administered once daily. At week 12, INCRUSE ELLIPTA statistically significantly increased the change from baseline in trough FEV_1 compared with placebo (Table 6). INCRUSE ELLIPTA also provided a statistically significant improvement compared with placebo in change from baseline in weighted mean FEV_1 over 0-6 hours post-dose at Day 1 and Day 84 [125 mL (95% CI=83 mL to 166 mL, p<0.001) and 166 mL (95% CI=94 mL to 239 mL, p<0.001), respectively].

Table 6 Primary efficacy endpoint at Week 12 (Day 85) for Treatment with INCRUSE ELLIPTA (62.5 mcg) in AC4115408

	Trough FEV_1 (mL) at Week 12 (Day 85)		
	Difference from Placebo		
	Treatment Difference	(95% CI)	p-value
INCRUSE ELLIPTA 62.5 mcg vs Placebo	127	(52,202)	<0.001

Abbreviations: CI= confidence interval; FEV_1= forced expiratory volume in 1 second; mL=milliliters

Serial FEV_1 improvements were statistically significant compared with placebo at each timepoint and were sustained over 24 hours on Day 1 and Day 84.

The pivotal placebo-controlled study (DB2113373) evaluated the efficacy of INCRUSE ELLIPTA compared with placebo, administered once daily. At week 24, INCRUSE ELLIPTA statistically significantly increased the change from baseline in trough FEV_1

compared with placebo (Table 7). INCRUSE ELLIPTA also provided a statistically significant improvement compared with placebo in change from baseline in weighted mean FEV_1 over 0-6 hours post-dose at week 24 (see Table 7).

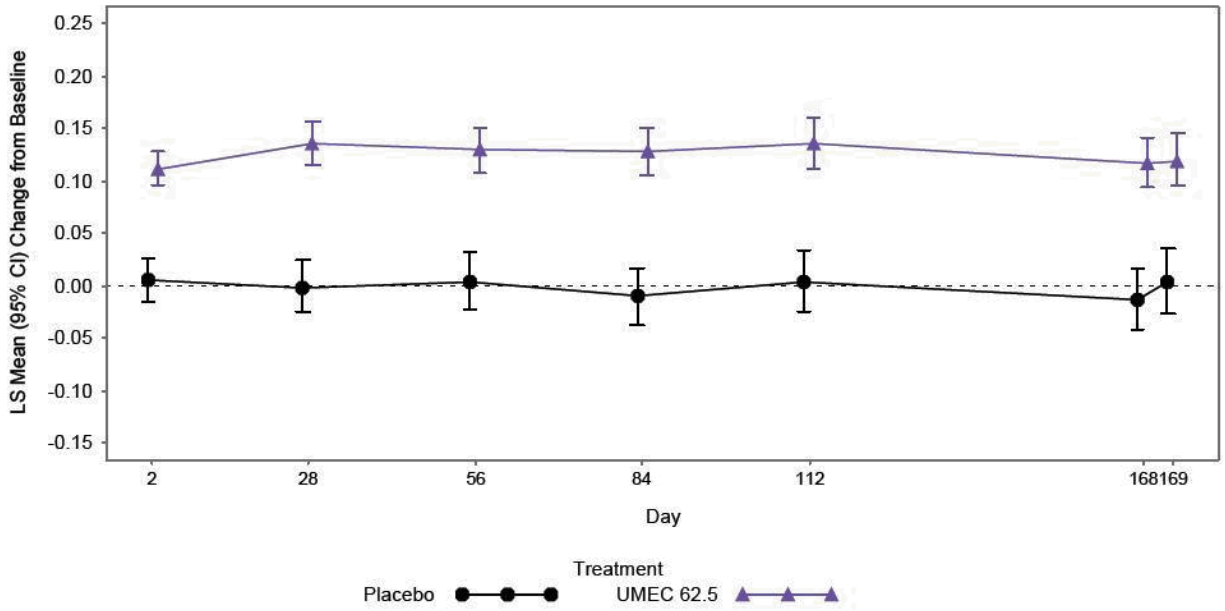
Table 7 Primary and Secondary Efficacy Endpoints at Week 24 for Treatment with INCRUSE ELLIPTA (62.5 mcg) in DB2113373

	Primary Endpoint		
	Trough FEV_1 (mL) at Day 169		
	Treatment Difference	**95% CI**	**p-value**
INCRUSE ELLIPTA 62.5 mcg vs Placebo	115	(76,155)	<0.001
	Secondary Endpoint		
	0-6 Hr Weighted Mean FEV_1 (mL) at Day 168		
	Treatment Difference	**95% CI**	**p-value**
INCRUSE ELLIPTA 62.5 mcg vs Placebo	150	(110,190)	<0.001

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; mL=milliliters

Greater bronchodilation with INCRUSE ELLIPTA compared with placebo was evident after the first day of treatment and improvement in lung function was maintained over the 24-week treatment period (Figure 1).

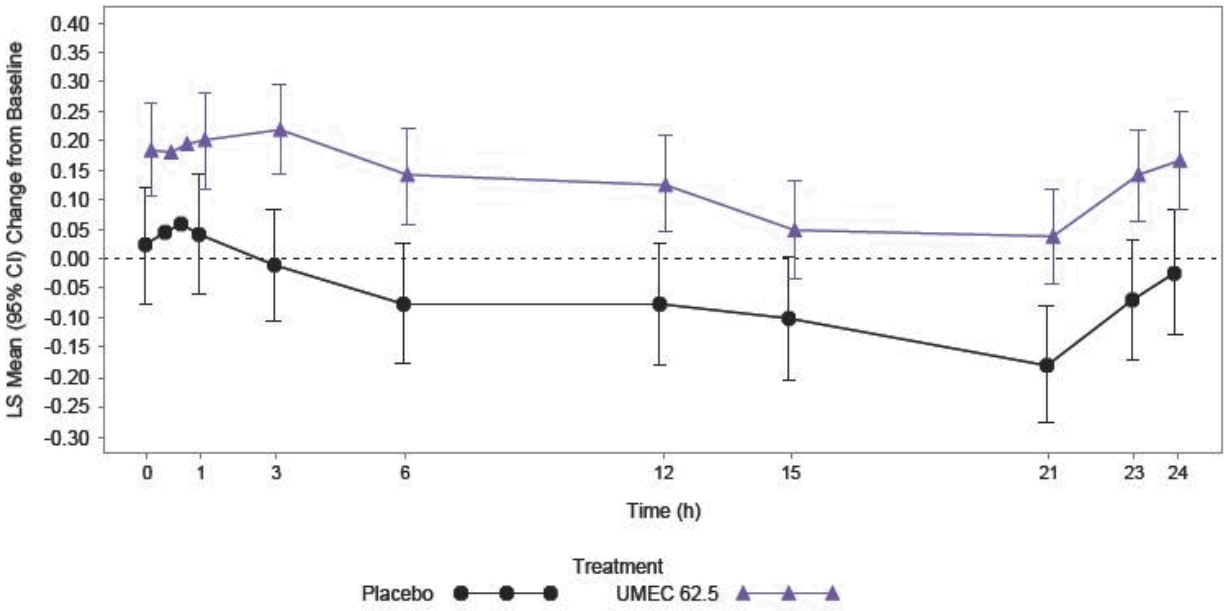
Figure 1 Least Squares (LS) Mean (95% CI) Change from Baseline in Trough FEV_1 (L) (DB2113373: Intent-to-Treat Population)



Serial spirometric evaluations throughout the 24-hour dosing interval were performed in a subset of subjects (n = 54, INCRUSE ELLIPTA 62.5 mcg; n = 36, placebo) at Days 1, 84, and 168. The median time to onset on Day 1, defined as a 100 mL increase from baseline in FEV_1 was 56 minutes in subjects receiving INCRUSE ELLIPTA.

Improvement in lung function from baseline was maintained for 24 hours after dosing (see Figure 2) and was consistent over Days 1, 84, and 168.

Figure 2 Least Squares (LS) Mean Change from Baseline in FEV_1 (L) Over Time (0-24 hr) on Day 168 (DB2113373: Subset Population)



Symptom Related Outcomes

In the pivotal placebo-controlled study, AC4115408, INCRUSE ELLIPTA demonstrated an improvement when compared with placebo in reducing shortness of breath, as measured by the TDI focal score at Week 12 (Day 84), although the improvement was not statistically significant (1.0 units; 95% CI=0.0 to 2.0). The percentage of patients that responded with minimum clinically important difference (MCID) of ≥1 unit TDI focal score at Week 12 (Day 84) for INCRUSE ELLIPTA was 38% (24/64) compared with 15% (8/53) for placebo.

In the pivotal placebo-controlled Study DB2113373, INCRUSE ELLIPTA demonstrated an improvement when compared with placebo in reducing shortness of breath, as measured by the TDI focal score at Week 24 (Day 168) (1.0 units; 95% CI=0.5 to 1.5). The percentage of patients that responded with MCID of ≥1 unit TDI focal score at Week 24 (Day 168) for INCRUSE ELLIPTA was 53% (207/394), compared with 41% (106/260) for placebo.

Health-related quality of life was measured using St. George's Respiratory Questionnaire (SGRQ) in both pivotal trials. In Study AC4115408 following 12 weeks of treatment, the mean difference from baseline in SGRQ total score between INCRUSE ELLIPTA and placebo was -7.90 units (95% CI=-12.20 to -3.60). More patients treated with INCRUSE

ELLIPTA had an improvement in SGRQ total score greater than the MCID (4 units) compared to placebo (44% vs. 26%).

In Study DB2113373, the mean difference in change from baseline in SGRQ total score between INCRUSE ELLIPTA and placebo at Day 28 and Day 168 was -5.15 units (95% CI=-6.89 to -3.4) and -4.69 units (95% CI=-7.07 to -2.31), respectively. Improvements from baseline with INCRUSE ELLIPTA were seen in all 3 SGRQ domains (symptoms, activities and impact; mean change from baseline on Day 168 was -10.97, -5.62 and -6.30 units, respectively). More patients treated with INCRUSE ELLIPTA had an improvement in SGRQ total score greater than the MCID (4 units) compared to placebo (44% vs. 34%).

In Study AC4115408, patients treated with INCRUSE ELLIPTA required less rescue salbutamol than those treated with placebo, with an average reduction of 0.7 puffs (95% CI=-1.3 to -0.1) per day. In Study DB2113373, patients treated with INCRUSE ELLIPTA required less rescue salbutamol than those treated with placebo, with an average reduction of 0.3 puffs per day, however the result was not statistically significant (95%CI = -0.8 puffs to 0.2 puffs) per day.

Exacerbations

In a randomised, double-blind, 52-week study (CTT116855) of 10,355 adult patients with COPD and a history of 1 or more moderate or severe exacerbations within the prior 12 months, treatment with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 100/62.5/25 mcg) once daily as a single inhaler was compared with a currently approved ICS/LABA once daily as a single inhaler. The primary endpoint was annual rate of on-treatment moderate and severe exacerbations in subjects treated with FF/UMEC/VI compared with ICS/LABA. The mean annual rate of exacerbations was 0.91 and 1.07 for FF/UMEC/VI and ICS/LABA, respectively.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacological and toxicological effects seen with umeclidinium in nonclinical studies were those typically associated with either muscarinic antagonists and/or local irritancy.

Human Pharmacology

Please refer to ACTION AND CLINICAL PHARMACOLOGY.

Clinical Pharmacology

Four 12-week additional trials (Combination with an ICS/LABA trials)

The efficacy of INCRUSE ELLIPTA in combination with an ICS/LABA was evaluated in four 12-week randomized, double-blind, parallel group trials in subjects with COPD. 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 in pivotal clinical studies. The primary endpoint for these trials was change from baseline in trough (pre-dose) 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.

Two trials randomized subjects to INCRUSE ELLIPTA 62.5 mcg + FF/VI 100/25 mcg administered once daily or placebo + FF/VI 100/25 mcg administered once daily. The results showed that patients treated with INCRUSE ELLIPTA 62.5 mcg + FF/VI 100/25 mcg had statistically significant greater mean changes from baseline in trough FEV_1 relative to placebo + FF/VI 100/25 mcg (124 mL; 95% CI: 93, 154 and 122 mL; 95% CI: 91, 152).

Similarly, two trials randomized subjects to INCRUSE ELLIPTA 62.5 mcg + FP/SAL 250/50 mcg or placebo + FP/SAL 250/50 mcg. The treatments with INCRUSE ELLIPTA and placebo were administered once daily, while the FP/SAL treatment was administered twice daily. The results showed that patients treated with INCRUSE ELLIPTA 62.5 mcg + FP/SAL 250/50 mcg had statistically significant greater mean changes from baseline in trough FEV_1 relative to placebo + FP/SAL 250/50 mcg (147 mL; 95% CI: 107, 187 and 127 mL; 95% CI: 89, 164).

In all four trials, the improvements of trough FEV_1 were supported by secondary efficacy endpoint of 0-6 hour weighted mean FEV_1 at Day 84; however, there were no differences in SGRQ among treatment groups, and the short duration of these studies and limited number of exacerbation events, preclude any conclusion regarding additional effect of INCRUSE ELLIPTA on COPD exacerbation.

TOXICOLOGY

Umeclidinium (UMEC) has undergone a comprehensive toxicological evaluation, and the principal findings are summarised in Table 8. In the majority of studies, UMEC was administered by the inhaled route which resulted in systemic exposure.

In repeat dose inhalation toxicity studies with UMEC, the principal treatment-related findings of relevance to risk assessment were irritant effects in the respiratory tract and expected pharmacology-related cardiovascular effects. In patients following repeated inhaled doses of 62.5 mcg/day plasma concentrations of UMEC were typically lower than those achieved in animal toxicology studies (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Table 8 Summary of Principal Findings in UMEC Toxicology Studies

Study Type & Duration	Route	Species	Dose (mcg/kg/day, unless indicated)	Noteworthy Findings
Single Dose	oral	mouse	100, 300, 1000 (mg/kg)	Single dose, acute inhaled toxicity studies have not been conducted with UMEC. However, in single dose tolerability studies, UMEC was well tolerated.
	intravenous subcutaneous	rat	5, 50 60	
Repeat Dose				Findings following repeated inhalation of high doses of UMEC to mice, rats, or dogs included deaths, severe clinical signs, body weight loss, reduction in food consumption and upper respiratory tract irritancy. Reductions in body weight gain were a relatively consistent observation across the nonclinical species following repeat dose inhaled administration. In dogs, the most consistent clinical signs were related to either pharmacology (e.g. dry eyes, nose and mouth) or were considered related to the method of dosing (e.g. excessive salivation). As expected from the pharmacology of muscarinic antagonists, a number of cardiovascular effects, including tachycardia, were also observed in dogs. UMEC was an irritant of the upper respiratory tract (nasal cavity/sinuses, nasopharynx, larynx and tracheal bifurcation) in mice, rats and dogs.
2 weeks	inhalation	mouse	299, 1080, 2690, 8110	
2 weeks (bridging)	inhalation	rat	1509, 1498, 1381	
		dog	1018, 1023, 1103	
13 weeks	inhalation	mouse	92, **287**, 1060, 2850	
		rat	38, 102, **288**, 924	
		dog	40.7, 187, **1070**	
26 weeks	inhalation	rat	**87.1**, 289, 987	
39 weeks	inhalation	dog	**109**, 421, 1002	

Study Type & Duration	Route	Species	Dose (mcg/kg/day, unless indicated)	Noteworthy Findings
				Gall bladder distension accompanied by myofibre degeneration/regeneration was observed in one 14 day dog study only and was not observed in longer term studies with either UMEC alone or in combination with VI. Effects in the lung (granuloma formation) observed in one dog study only were considered to be secondary to excessive antimuscarinic pharmacology. In the 6 month rat study with UMEC, there was variation in incidence of non-foamy, non-degenerative macrophages across groups, including controls, with a small shift in severity grading only at the high dose in male rats. In addition, ventral cartilage degeneration/necrosis of the larynx was also observed. The test-article relationship of the arterial changes in the heart and lungs (inflammation of the external coronary arteries and pulmonary arteriole) in the dog 39 week study could not be established. At the NOAEL in repeat dose toxicity studies of up to 39 weeks duration, compared with systemic exposures seen in COPD subjects receiving 62.5 mcg/day UMEC[a], AUC exposures were 18X in mice, ≥26X greater in rats, and ≥36X in dogs.
Genotoxicity Ames Mouse Lymphoma	*in vitro*	NA*	up to 5000 mcg/plate up to 225 mcg/mL	There was no evidence of genotoxicity in in vitro assays (Ames test and Mouse Lymphoma assay) or in the in vivo micronucleus test in rats.
Micronucleus (2 doses, 24 hours apart)	intravenous	rat	10000, 20000	
Carcinogenicity 104 weeks	inhalation	mouse	M: 58.6/32.2[b], 188/102[b], 533/295[b] F: 20.8, 63.7, 200	There was no evidence of treatment-related increases in tumour incidence in two year inhalation studies in rats and mice.
		rat	30.1/14.7[c], 101/45.0[c], 276/137[c]	

Study Type & Duration	Route	Species	Dose (mcg/kg/day, unless indicated)	Noteworthy Findings
Reproductive Toxicity Male fertility 49 to 53 days (from 14 days prior to mating)	subcutaneous	rat	30, 60, **180**	UMEC was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of UMEC to rats resulted in lower maternal body weight gain and food consumption and slightly decreased pre-weaning pup body weights in dams given 180 micrograms/kg/day dose. Based on systemic exposure data at a similar dose used in 13 week repeat-dose toxicity study in rats, at the developmental NOAEL, exposures were approximately 52X those achieved in subjects with COPD given 62.5 mcg/day UMEC[a]; in rabbits, the NOAEL following subcutaneous administration was 197X and 35X following inhaled administration.
FFEED[2] 22 to 27 days (from 2 weeks prior to mating to Day 7 pc)	inhalation	rat	3.37, 29.1, 100, **294**	
EFD[3] 12 days (from Days 6 to 17 pc)	inhalation	rat	32.0, 96.9, **278**	
13 days (from Days 7 to 19 pc)	Inhalation subcutaneous	rabbit	28.5, 88.9, **306** 40, 100, **180**	
PPN[4] 35 days (from Day 6 pc to Day 20 pp)	subcutaneous	rat	10, 60, **180**	
Local Tolerance Hemolysis	*in vitro*	rat dog human	up to 0.01 mg/mL	No or negligible hemolysis was evident in rat, dog and human blood treated with UMEC. UMEC was considered to be a non-sensitiser. UMEC was considered to be a mild/moderate dermal irritant using a reconstituted human skin model. UMEC was considered to be a mild/moderate ocular irritant using a reconstituted human epidermal model.
Local lymph node assay	topical	mouse	25 mcL of 25% (w/w) per ear	
Dermal irritancy	topical	rabbit	0.5 mL per site of 0.5%, 1% or 2% solution	
Dermal irritancy	topical	NA*	25 mg	
Ocular irritancy	topical	NA*	30 mg	
Other Toxicity **Genotoxicity[d]** Ames	*in vitro*	NA*	up to 5000 mcg/plate	GW377650X did not cause gene mutations in bacteria. GR130510X, GR59413X and GW348594X did cause gene mutations in bacteria in either the presence or absence of S9-mix.

Key:
a = Model predicted geometric mean systemic exposure following administration of 62.5 mcg UMEC in subjects with COPD = 0.0693 ng/mL (C_{max}) or 0.3124 ng.h/mL (AUC)
b = From Week 67 onwards, the dose was reduced for male mice from 58.6 to 32.2 mcg/kg/day, from 188 to

Study Type & Duration	Route	Species	Dose (mcg/kg/day, unless indicated)	Noteworthy Findings
102 mcg/kg/day and from 533 to 295 mcg/kg/day c = From Week 73 onwards, the dose was reduced for rats from 30.1 to 14.7 mcg/kg/day, from 101 to 45.0 mcg/kg/day and from 276 to 137 mcg/kg/day d = Intermediates used in the synthesis of GSK573719. *NA = Not applicable; [2]FFEED = Female fertility and early embryonic development; [3]EFD = Embryofoetal development; [4]PPN =Pre- and post-natal development; pc = post-coitum; pp = post partum; M = Male; F = Female Where applicable, the NOAEL is identified as underlined and bold text.				

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1. Donohue, J.F., Maleki-Yazdi, M.R., Kilbride, S., Mehta, R., Kalberg, C.J., Church, A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. Respiratory Medicine 2013; 107:1538-1546.
2. Triverdi R., Richard N., Metha R., Church A. Umeclidinium in patients with COPD: a randomised placebo-controlled study. *European Respiratory Journal* 2014; 43:72-81.

PART III: CONSUMER INFORMATION

PrINCRUSE ELLIPTA
umeclidinium (as bromide) dry powder for oral inhalation

This leaflet is part III of a three-part "Product Monograph" published when INCRUSE ELLIPTA was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about INCRUSE ELLIPTA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

INCRUSE ELLIPTA is used as a long-term, once a day maintenance treatment. It can make breathing easier for people who experience breathing difficulties (i.e., shortness of breath) due to a lung disease called Chronic Obstructive Pulmonary Disease or COPD (including chronic bronchitis and emphysema).

If you are a smoker, it is important to quit smoking. This will help decrease the symptoms of COPD and potentially increase your lifespan.

What it does:

INCRUSE ELLIPTA is a long-acting muscarinic antagonist (LAMA).

INCRUSE ELLIPTA relaxes the muscles in the walls of small airways in the lungs. This medicine works to help open the airways and make it easier for air to get in and out of the lungs. When taken regularly, INCRUSE ELLIPTA helps keep the airways open, which can help prevent shortness of breath and wheezing.

There is no cure for COPD, but INCRUSE ELLIPTA helps to control it. It is therefore important that you continue to take INCRUSE ELLIPTA regularly even if you feel fine.

When it should not be used:

Do not use INCRUSE ELLIPTA:

- To treat sudden severe symptoms of COPD such as sudden shortness of breath or wheezing. If you experience this sort of attack you must use a rapid onset, short duration, inhaled bronchodilator such as salbutamol (rescue medication). Keep this rescue medication with you at all times.
- If you are allergic to any of the medicinal or nonmedicinal ingredients contained in the product.
- If you have a lactose or severe milk protein allergy.
- If you are younger than 18 years of age.

What the medicinal ingredient is:

Umeclidinium.

What the nonmedicinal ingredients are:

Lactose monohydrate (which contains milk proteins) and magnesium stearate.

What dosage forms it comes in:

Dry powder for oral inhalation delivered by the ELLIPTA inhaler. Each dose contains 62.5 mcg umeclidinium per blister.

Each inhaler contains one month's supply (one dose per day for 30 days).

If a sample is given to you by your doctor, it will contain one week's supply (one dose per day for 7 days).

WARNINGS AND PRECAUTIONS

BEFORE you use INCRUSE ELLIPTA talk to your doctor or pharmacist if you have any of the following:

- Heart problems.
- Eye problems such as increased pressure in the eye, or glaucoma.
- Prostate or bladder problems, or problems passing urine.
- Any allergies to food or drugs.

Pregnancy and breast-feeding:

If you are pregnant, or think you could be, or if you are planning to become pregnant, don't take INCRUSE ELLIPTA without asking your doctor. Your doctor will consider the benefit to you and the risk to your unborn baby.

It is not known whether the ingredients of INCRUSE ELLIPTA can pass into breast milk. If you are breast-feeding, check with your doctor before you take INCRUSE ELLIPTA.

Driving and Using Machines:
If you experience side effects such as dizziness or blurred vision, you should avoid driving or operating machinery.

COPD flare-up:
INCRUSE ELLIPTA should not be used to relieve a COPD

flare-up. If you experience this sort of attack you must use a rapid onset, short duration, inhaled bronchodilator such as salbutamol (i.e. rescue medication).

If you notice any of the following symptoms, tell your doctor immediately. They could be warning signs that you are having a COPD flare-up or your condition is worsening.

- Unusual increase in the severity of breathlessness, cough, wheezing, or fatigue.
- Unusual colour, amount or thickness of mucus.
- Tightness in the chest or symptoms of a cold.
- You need to use your rescue medication more often than usual.
- Your rescue medication does not work as well to relieve your symptoms.

Short-acting bronchodilators should only be used as rescue medication while you are taking INCRUSE ELLIPTA. Your doctor will instruct you on how to discontinue their **regular** use when you start taking INCRUSE ELLIPTA.

This medication has been prescribed for you and should not be given to other people.

INTERACTIONS WITH THIS MEDICATION

Be sure to tell your doctor or pharmacist:

- About any medicines you are currently taking, or have taken recently, including medications that did not require a prescription, e.g. alternative medicines, vitamins and minerals.
- If you start any new medications.

Drugs that may interact with INCRUSE ELLIPTA include:

- Other medications that contain a short- or long-acting muscarinic antagonist (e.g. ipratropium, tiotropium, glycopyrronium, aclidinium). Ask your doctor or pharmacist if any of your other medicines are ipratropium or LAMA containing medicines.

PROPER USE OF THIS MEDICATION

If you have any difficulties or you are unsure about how or when to take INCRUSE ELLIPTA, check with your doctor or pharmacist.

One dose of INCRUSE ELLIPTA lasts a full 24 hours.
Take INCRUSE ELLIPTA:

- Exactly as recommended by your doctor
- Only once a day
- At the same time each day
- By inhaling it into the lungs through the mouth

Unless you talk to your doctor first, **DO NOT**:

- Stop taking INCRUSE ELLIPTA (even if you feel better)
- Use it more frequently than once a day
- Increase the dose

Usual Adult Dose:
One inhalation through the mouth once a day.

Taking INCRUSE ELLIPTA at the same time every day will help you remember to use it.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

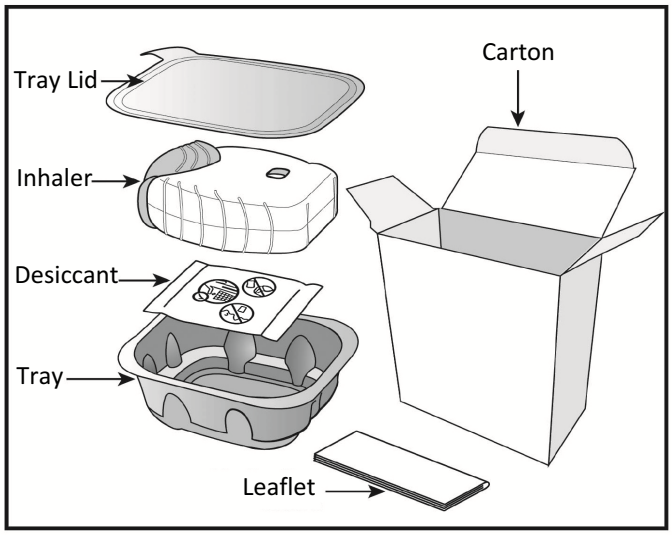
If you accidentally take a larger dose of INCRUSE ELLIPTA (i.e., more drug than recommended by your doctor), you may have a headache, dry mouth, blurred vision, or feel like your heart is beating faster than usual. Talk to your doctor or pharmacist right away if this occurs.

Missed Dose:

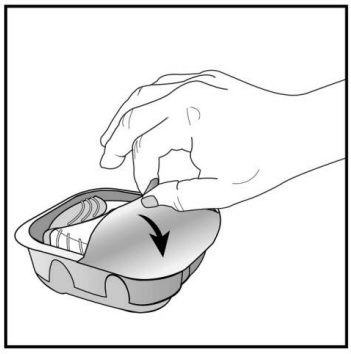
If you miss a dose, take your next dose at the usual time the next day. Do not take an extra dose to make up for a missed one.

About your INCRUSE ELLIPTA Inhaler:

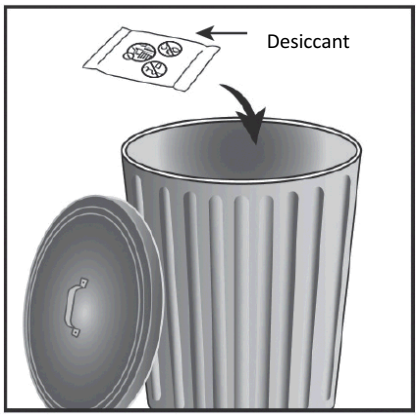
Your ELLIPTA inhaler carton contains:



The plastic ELLIPTA inhaler is packaged in a tray, with a peelable foil lid. **Do not remove the foil lid until you are ready to use the inhaler.** Peel back the lid to open the tray.



In the tray, you will find a small desiccant sachet containing a drying agent. The desiccant sachet helps to prevent moisture from forming inside the tray. **Keep it away from children and pets.** Do **not** open, eat or inhale the desiccant sachet and **throw it away** once you have opened the lid of the tray. It is dangerous to eat or inhale the contents of the desiccant sachet.



When you take your ELLIPTA inhaler out of its tray it will be in the closed position. Write the "Discard by" date on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date you open the tray.

The plastic ELLIPTA inhaler has a light grey body, a light green mouthpiece cover, and a dose counter. The mouthpiece and the air vent are hidden by the cover and can only be seen when the cover is opened. The ELLIPTA inhaler is ready-to-use. You will not need to prime it before using it for the first time.

Cover

Each time you open this, you prepare one dose of medicine.

Dose Counter

This shows how many doses of medicine are left in the inhaler.

Before the inhaler has been used, it shows exactly 30 doses (7 for

IMPORTANT:
If you open and close the cover of the ELLIPTA inhaler without inhaling the medicine, you will lose a dose. The dose will be securely held inside the inhaler, but it will no longer be available. It is not possible to accidently take extra medicine or take a double dose in one inhalation.

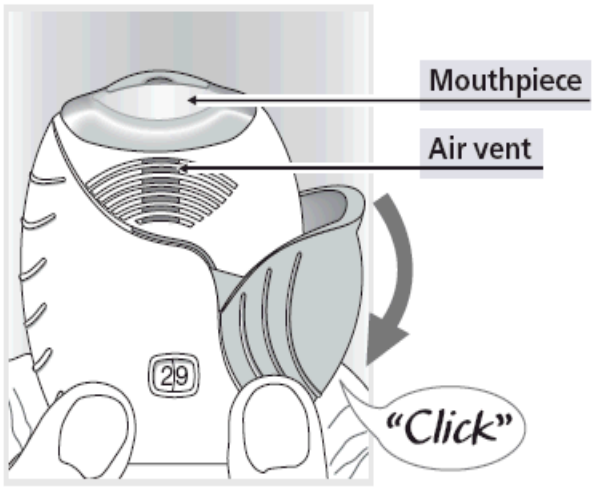
Never try to alter the numbers on the counter or detach the counter on the front of the ELLIPTA inhaler. The counter cannot be reset and is permanently attached to the inhaler.

How to use INCRUSE ELLIPTA
Please follow the instructions '**OPEN, INHALE, and CLOSE**' to use your ELLIPTA inhaler. The instructions shown below apply to both the 30-dose and 7-dose ELLIPTA inhaler.

Keep the cover closed until you are ready to inhale a dose. Do not shake the ELLIPTA inhaler at any point during use as this is not necessary.

Sit down or stand in a comfortable position.

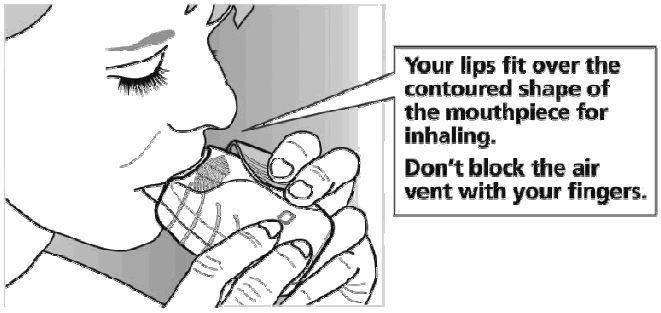
OPEN:
1. When you are ready, activate the inhaler by sliding the light green cover down until you hear a 'click' to prepare a dose.
2. The dose counter will now count down by one number ("1"). *It is unlikely the dose counter will not count down as you hear the 'click'. If this happens, it may mean the inhaler did not load the medicine. Bring it back to your pharmacist for advice.*
3. While holding the inhaler away from your mouth, exhale a complete breath (i.e. breathe out as far as is comfortable). *Don't breathe out into the inhaler.*



You are now ready to inhale a dose.

INHALE:

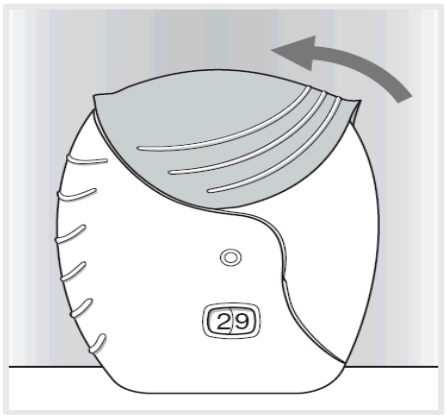
1. Put the mouthpiece between your lips, and close your lips firmly around it. *Don't block the air vent with your fingers.*



2. Take one long, steady, deep breath in. Hold this breath for as long as possible (minimum 3-4 seconds).

CLOSE:

1. Remove the inhaler from your mouth. Exhale slowly and gently. Continue to breathe normally.
2. You can clean the mouthpiece of the inhaler with a clean dry tissue after you have inhaled the medicine.
3. Close the inhaler by sliding the cover upwards as far as it will go to cover the mouthpiece.



You may not be able to taste or feel the medicine (this is normal), even when you are using the inhaler correctly.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- cough
- diarrhea, stomach pain
- constipation
- pain in arms and legs, neck pain, back pain
- headache
- feeling of pressure or pain in the cheeks and forehead (may be signs of inflammation of the sinuses called sinusitis), runny nose, sore throat
- dry mouth, toothache, taste disturbance
- feeling dizzy
- joint pain, muscle pain
- nausea
- depression
- common cold
- bruising

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Common	**Fast heartbeat**		✓	
Uncommon	**Pneumonia** (an infection of the lungs): Fever, chills, increase in sputum production, change in sputum colour, increased cough or an increase in breathing difficulties (shortness of breath, chest pain).		✓	
	Irregular heartbeat		✓	
	Allergic reaction: Skin rash, hives, redness, swelling of the face, lips, tongue or throat (angioedema), becoming very wheezy, coughing or difficulty swallowing or breathing; suddenly feeling weak or light headed (may lead to collapse or loss of consciousness).			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Unknown	**Eye disorders:** Decrease in vision, or new or worsened pressure in your eyes (possible signs of glaucoma), eye pain or discomfort, blurred vision, seeing halos or rainbows around items or red eyes			✓
	Paradoxical bronchospasm (worsening of symptoms related to breathing): Tightness of the chest associated with coughing, or breathlessness immediately after inhalation of INCRUSE ELLIPTA			✓
	Difficulty urinating or urinary infection: Difficulty and pain when passing urine, urinating frequently, urination in a weak stream or drips		✓	

This is not a complete list of side effects. For any unexpected effects while taking INCRUSE ELLIPTA, contact your doctor or pharmacist.

HOW TO STORE IT

- **Keep out of sight and reach of children. Your medicine may harm them.**
- **Keep your inhaler in a cool dry place away from direct heat or sunlight.** Keep it closed when not in use.
- Do not store INCRUSE ELLIPTA in areas above 30°C. If you store in a refrigerator, **allow the inhaler to return to room temperature for at least an hour** before use.
- Store in the original package in order to protect from moisture and do not open the foil lid until ready for first use.
- Once the tray is opened:
  - You can use the inhaler for up to 6 weeks, starting from the date you opened the lid of the tray.
  - Write the date the inhaler should be discarded on the inhaler in the space provided.
- Safely discard INCRUSE ELLIPTA when the dose counter reads "0" or 6 weeks after you open the lid of the tray, whichever comes first. **INCRUSE ELLIPTA expires 6 weeks after you have opened the lid of the tray.**

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

You may need to read this package insert again. **Please do not throw it away** until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.gsk.ca or by contacting the sponsor,

GlaxoSmithKline Inc.
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L5N 6L4
1-800-387-7374

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