

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Incruse 55 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece of the inhaler) of 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) This corresponds to a pre-dispensed dose of 62.5 micrograms umeclidinium equivalent to 74.2 micrograms umeclidinium bromide.

Excipient with known effect:

Each delivered dose contains approximately 12.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed (inhalation powder).

White powder in a grey inhaler (Ellipta) with a light green mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Incruse is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

4.2 Posology and method of administration

Posology

Adults

The recommended dose is one inhalation of umeclidinium bromide once daily.

Incruse should be administered once daily at the same time of the day each day to maintain bronchodilation. The maximum dose is one inhalation of umeclidinium bromide once daily.

Special populations

Elderly patients

No dosage adjustment is required in patients over 65 years (see section 5.2).

Renal impairment

No dosage adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. Incruse has not been studied in patients with severe hepatic impairment and should be used with caution (see section 5.2).

Paediatric population

There is no relevant use of Incruse in the paediatric population (under 18 years of age) in the indication for COPD.

Method of administration

Incruse is for inhalation use only.

Instructions for use:

The following instructions for the 30 dose inhaler (30 day supply) also apply to the 7 dose inhaler (7 day supply).

The Ellipta inhaler contains pre-dispensed doses and is ready to use.

The inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. The desiccant sachet should be thrown away and it should not be opened, eaten or inhaled.

The patient should be advised to not open the tray until they are ready to inhale a dose.

The inhaler will be in the 'closed' position when it is first taken out of its sealed tray. The "Discard by" date should be written on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date of opening the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

If the inhaler cover is opened and closed without inhaling the medicinal product, the dose will be lost. 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 extra medicine or a double dose in one inhalation.

a) Prepare a dose

Open the cover when ready to take a dose. The inhaler should not be shaken.

Slide the cover down until a "click" is heard. The medicinal product is now ready to be inhaled.

The dose counter counts down by 1 to confirm. If the dose counter does not count down as the "click" is heard, the inhaler will not deliver a dose and should be taken back to a pharmacist for advice.

b) How to inhale the medicinal product

The inhaler should be held away from the mouth breathing out as far as is comfortable. But not breathing out into the inhaler.

The mouthpiece should be placed between the lips and the lips should then be closed firmly around it. The air vents should not be blocked with fingers during use.

- Inhale with one long, steady, deep breath in. This breath should be held in for as long as possible (at least 3-4 seconds).
- Remove the inhaler from the mouth.
- Breathe out slowly and gently.

The medicine may not be tasted or felt, even when using the inhaler correctly.

The mouthpiece of the inhaler may be cleaned using a **dry tissue before** closing the cover.

c) **Close the inhaler**

Slide the cover upwards as far as it will go, to cover the mouthpiece.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Asthma

Umeclidinium bromide should not be used in patients with asthma since it has not been studied in this patient population.

Paradoxical bronchospasm

Administration of umeclidinium bromide may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.

Deterioration of disease

Umeclidinium bromide is intended for the maintenance treatment of COPD. It should not be used for the relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting bronchodilator. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control. In the event of deterioration of COPD during treatment with umeclidinium bromide, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists including umeclidinium bromide. In addition, patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium bromide should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.

Antimuscarinic activity

Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Other antimuscarinics

Co-administration of umeclidinium bromide with other long-acting muscarinic antagonists or medicinal products containing this active substance has not been studied and is not recommended as it may potentiate known inhaled muscarinic antagonist adverse reactions.

Metabolic and transporter based interactions

Umeclidinium bromide is a substrate of cytochrome P450 2D6 (CYP2D6). The steady-state pharmacokinetics of umeclidinium bromide were assessed in healthy volunteers lacking CYP2D6 (poor metabolisers). No effect on umeclidinium AUC or C_{max} was observed at a dose 4-fold higher than the

therapeutic dose. An approximately 1.3-fold increase in umeclidinium bromide AUC was observed at an 8-fold higher dose with no effect on umeclidinium bromide C_{max} . Based on the magnitude of these changes, no clinically relevant drug interaction is expected when umeclidinium is co-administered with CYP2D6 inhibitors or when administered to subjects genetically deficient in CYP2D6 activity (poor metabolisers).

Umeclidinium bromide is a substrate of P-glycoprotein (P-gp) transporter. The effect of the moderate P-gp inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium bromide was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium bromide C_{max} . An approximately 1.4-fold increase in umeclidinium bromide AUC was observed. Based on the magnitude of these changes, no clinically relevant interaction is expected when umeclidinium bromide is co-administered with P-gp inhibitors.

Other medicinal products for COPD

Although no formal *in vivo* interaction studies have been performed, inhaled umeclidinium bromide has been used concomitantly with other COPD medicinal products including short and long acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of umeclidinium bromide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Umeclidinium bromide should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

Breast-feeding

It is unknown whether umeclidinium bromide is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue Incruse therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of umeclidinium bromide on human fertility. Animal studies indicate no effects of umeclidinium bromide on fertility.

4.7 Effects on ability to drive and use machines

Umeclidinium bromide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions with Incruse were nasopharyngitis and upper respiratory tract infection.

Tabulated summary of adverse reactions

The safety profile of umeclidinium bromide was evaluated from 1663 patients with COPD who received doses of 55 micrograms or greater for up to one year. This includes 576 patients who received the recommended dose of 55 micrograms once daily.

The frequencies assigned to the adverse reactions identified in the table below include crude incidence rates observed from four efficacy studies and the long-term safety study (which involved 1,412 patients who received umeclidinium bromide).

The frequency of adverse reactions is defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from available data).

System Organ Class	Adverse reactions	Frequency
Infections and infestations	Nasopharyngitis Upper respiratory tract infection Urinary tract infection Sinusitis Pharyngitis	Common Common Common Common Uncommon
Immune system disorders	Hypersensitivity reactions including: Rash, urticaria and pruritus	Uncommon
Nervous system disorders	Headache Dysgeusia	Common Uncommon
Eye disorders	Glaucoma Vision blurred Eye pain Intraocular pressure increased	Not known Not known Rare Not known
Cardiac disorders	Atrial fibrillation Rhythm idioventricular Supraventricular tachycardia Supraventricular extrasystoles Tachycardia	Uncommon Uncommon Uncommon Uncommon Common
Respiratory, thoracic and mediastinal disorders	Cough	Common
Gastrointestinal disorders	Constipation Dry mouth	Uncommon Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
Renal and urinary disorders	Urinary retention Dysuria	Not known Not known

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

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

If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, anticholinergics, ATC code: R03BB07

Mechanism of action

Umeclidinium bromide is a long acting muscarinic receptor antagonist (also referred to as an anticholinergic). It is a quinuclidine derivative that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Umeclidinium bromide exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic cholinergic 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.

Pharmacodynamic effects

In a Phase III, 6-month study (DB2113373) Incruse provided a clinically meaningful improvement over placebo in lung function (as measured by forced expiratory volume in 1 second [FEV₁]) over 24 hours following once daily administration, which was evident at 30 minutes following administration of the first dose (improvement over placebo by 102 mL, p<0.001*). The mean peak improvements in FEV₁ within the first 6 hours following dosing relative to placebo were 130 ml (p<0.001*) at Week 24. There was no evidence for tachyphylaxis in the effect of Incruse over time.

Cardiac electrophysiology

The effect of umeclidinium 500 micrograms (pre-dispensed) on the QT interval was evaluated in a placebo- and moxifloxacin-controlled QT trial of 103 healthy volunteers. Following repeat doses of umeclidinium 500 micrograms once daily for 10 days, no clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) or effects on heart rate were observed.

Clinical efficacy

The clinical efficacy of Incruse administered once daily was evaluated in 904 adult patients who received umeclidinium bromide or placebo from two pivotal Phase III clinical studies with a clinical diagnosis of COPD; a 12-week study (AC4115408) and a 24-week study (DB2113373).

Pivotal Efficacy Studies:

Effects on lung function

In both of the pivotal 12-week and 24-week studies, Incruse demonstrated statistically significant and clinically meaningful improvements in lung function (as defined by change from baseline trough FEV₁ at Week 12 and Week 24 respectively, which was the primary efficacy endpoint in each study) compared with placebo (see *Table 1*). The bronchodilatory effects with Incruse compared with placebo were evident after the first day of treatment in both studies and were maintained over the 12-week and 24-week treatment periods.

There was no attenuation of the bronchodilator effect over time.

Table 1: Trough FEV₁ (ml) at Week 12 and Week 24 (primary endpoint)

Treatment with Incruse 55 mcg	12-Week Study Treatment difference¹ 95% Confidence interval p-value	24-Week Study Treatment difference¹ 95% Confidence interval p-value
Versus Placebo	127 (52, 202) <0.001	115 (76, 155) <0.001

mcg = micrograms

¹least squares mean (95% confidence interval)

Incruse demonstrated a statistically significant greater improvement from baseline in weighted mean FEV₁ over 0-6 hours post-dose at Week 12 compared with placebo (166 ml, p<0.001) in the 12-week pivotal study. Incruse demonstrated a greater improvement from baseline in weighted mean FEV₁ over 0-6 hours post-dose at Week 24 compared with placebo (150 ml, p<0.001*) in the 24-week pivotal study.

Symptomatic outcomes

Breathlessness:

In the 12-week study, a statistically significant improvement compared with placebo in the TDI focal score at Week 12 was not demonstrated for Incruse (1.0 units, p=0.05). A statistically significant improvement compared with placebo in the TDI focal score at Week 24 was demonstrated for Incruse (1.0 units, p<0.001) in the 24-week study.

The proportion of patients who responded with at least the minimum clinically important difference (MCID) of 1 unit TDI focal score at Week 12 was greater for Incruse (38%) compared with placebo (15%) in the 12-week study. Similarly, a greater proportion of patients achieved ≥1 unit TDI focal score for Incruse (53%) compared with placebo (41%) at Week 24 in the 24-week study.

Health-related quality of life:

Incruse also demonstrated a statistically significant improvement in health-related quality of life measured using the St. George's Respiratory Questionnaire (SGRQ) as indicated by a reduction in SGRQ total score at Week 12 compared with placebo (-7.90 units, p<0.001) in the 12-week study. A greater improvement compared with placebo in the change from baseline in SGRQ total score at Week 24 was demonstrated for Incruse (-4.69 units, p<0.001*) in the 24-week study.

The proportion of patients who responded with at least the MCID in SGRQ score (defined as a decrease of 4 units from baseline) at Week 12 was greater for Incruse 55 micrograms (44%) compared with placebo (26%) in the 12-week study. Similarly, a greater proportion of patients achieved at least the MCID for Incruse at Week 24 (44%) compared with placebo (34%) in the 24-week study.

COPD exacerbations

In the 24-week study, Incruse lowered the risk of a COPD exacerbation compared with placebo (analysis of time to first exacerbation; Hazard Ratio 0.6, p=0.035*). The probability of having an exacerbation in patients receiving Incruse at week 24 was 8.9% compared with 13.7% for placebo. These studies were not specifically designed to evaluate the effect of treatments on COPD exacerbations and patients were withdrawn from the study if an exacerbation occurred.

*A step-down statistical testing procedure was used in this study and this comparison was below a comparison that did not achieve statistical significance. Therefore, statistical significance on this comparison cannot be inferred.

*A step-down statistical testing procedure was used in this study and this comparison was below a comparison that did not achieve statistical significance. Therefore, statistical significance on this comparison cannot be inferred.

Use of rescue medicinal product

In the 12-week study, Incruse statistically significantly reduced the use of rescue medication with salbutamol compared with placebo (on average a reduction of 0.7 puffs per day over Weeks 1-12, $p=0.025$) and demonstrated a higher percentage of days when no rescue medication was needed (on average 46.3%) compared with placebo (on average 35.2%; no formal statistical analysis was performed on this endpoint). In the 24-week study treatment with Incruse, the mean (SD) change from baseline in the number of puffs of rescue salbutamol over the 24-week treatment period was -1.4 (0.20) for placebo and -1.7 (0.16) for Incruse (Difference = -0.3; 95% CI: -0.8, 0.2, $p=0.276$). Patients receiving Incruse had a higher percentage of days when no rescue medication was needed (on average 31.1%) compared with placebo (on average 21.7%). No formal statistical testing was performed on this endpoint.

Supporting efficacy studies

In two 12-week, placebo controlled studies (200109 and 200110), the addition of Incruse to fluticasone furoate/vilanterol (FF/VI) (92/22 micrograms) once daily in adult patients with a clinical diagnosis of COPD, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV₁ at Day 85 compared to placebo plus FF/VI (124 mL (95% CI 93, 154, $p<0.001$) and 122 mL (95% CI 91, 152, $p<0.001$)).

Improvements in lung function were supported with reductions in use of salbutamol over Weeks 1-12 (-0.4 puffs per day (95% CI -0.7, -0.2, $p<0.001$) and -0.3 puffs per day (95% CI -0.5, -0.1, $p=0.003$)) compared to placebo plus FF/VI but improvements in SGRQ at week 12 were not statistically significant (200109) or clinically relevant (200109 and 200110). The short duration of the studies and limited number of exacerbation events, preclude any conclusion regarding additional effect of Incruse on COPD exacerbation rate.

No new adverse drug reactions were identified with the addition of Incruse to FF/VI in these studies.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Incruse in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Following inhaled administration of umeclidinium bromide in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled umeclidinium bromide was on average 13% of the dose, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium bromide, steady state was achieved within 7 to 10 days with 1.5 to 1.8-fold accumulation.

Distribution

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

Biotransformation

In vitro studies showed that umeclidinium bromide is principally metabolised by cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium bromide are oxidative (hydroxylation, O-dealkylation) followed by conjugation (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.

Elimination

Plasma clearance following intravenous administration was 151 litres/hour. Following intravenous administration, approximately 58% of the administered radiolabelled dose (or 73% of the recovered radioactivity) was excreted in faeces by 192 hours post-dose. Urinary elimination accounted for 22% of the administered radiolabelled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male subjects, total radioactivity was excreted primarily in faeces (92% of the administered radiolabelled dose or 99% of the recovered radioactivity) by 168 hours post-dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium bromide plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% active substance excreted unchanged in urine at steady-state.

Characteristics in specific groups of subjects or patients

Elderly

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

Renal impairment

Subjects with severe renal impairment (creatinine clearance <30mL/min) showed no evidence of an increase in systemic exposure to umeclidinium bromide (C_{max} and AUC), and no evidence of altered protein binding between subjects with severe renal impairment and healthy volunteers.

Hepatic impairment

Subjects with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to umeclidinium bromide (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium bromide has not been evaluated in subjects with severe hepatic impairment.

Other special populations

A population pharmacokinetic analysis showed that no dose adjustment is required for umeclidinium bromide based on the effect of age, race, gender, inhaled corticosteroid use or weight. A study in CYP2D6 poor metabolisers showed no evidence of a clinically significant effect of CYP2D6 genetic polymorphism on systemic exposure to umeclidinium bromide.

5.3 Preclinical safety data

Non clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In nonclinical studies with umeclidinium bromide, findings were those typically associated with the primary pharmacology of muscarinic receptor antagonists and/or local irritancy.

Reproductive toxicity

Umeclidinium bromide was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium bromide 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 (approximately 80-times the human clinical exposure of umeclidinium 55 micrograms, based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,

Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

In-use shelf-life after opening the tray: 6 weeks.

6.4 Special precautions for storage

Do not store above 30°C. If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

Keep the inhaler inside the sealed tray in order to protect from moisture and only remove immediately before first use.

To be used within 6 weeks of first opening of the tray.

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.

6.5 Nature and contents of container

The Ellipta inhaler consists of a grey body, light green mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant packet. The tray is sealed with a peelable foil lid.

The inhaler contains one aluminium foil laminate blister of 7 or 30 doses.

The inhaler is a multi-component device composed of polypropylene, high density polyethylene, polyoxymethylene, polybutylene terephthalate, acrylonitrile butadiene styrene, polycarbonate and stainless steel.

Pack sizes of 7 and 30 dose inhaler.

Multipack of 3 x 30 dose inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

For instructions for handling, see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road,
Brentford,
Middlesex,

TW8 9GS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/922/001
EU/1/14/922/002
EU/1/14/922/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 April 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Glaxo Operations UK Ltd. (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Hertfordshire SG12 0DJ
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
Submission of the final clinical study report on a Post-Authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients with Incruse compared with tiotropium (study 201038), according to a protocol agreed by the PRAC.	By Q3 2024

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (SINGLE PACKS & MULTIPACK ONLY)

55 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Incruse 55 micrograms inhalation powder, pre-dispensed
umeclidinium (umeclidinium bromide)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide).

3. LIST OF EXCIPIENTS

Also contains lactose and magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed.

7 doses

30 doses

3 x 30 doses

1 inhaler (Ellipta) of 7 doses.

1 inhaler (Ellipta) of 30 doses.

Multipack: 90 (3 Ellipta inhalers of 30) doses - 3 × 30 doses.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use, ONCE DAILY

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

In use shelf-life: 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom

Glaxo Group Ltd logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/922/001 1 inhaler (Ellipta) of 7 doses

EU/1/14/922/002 1 inhaler (Ellipta) of 30 doses

EU/1/14/922/003 Multipack: 90 (3 Ellipta inhalers of 30) doses - 3 × 30 doses

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

incruse ellipta

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:

NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE OUTER CARTON (WITHOUT BLUE BOX- MULTIPACK ONLY)

55 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Incruse 55 micrograms inhalation powder, pre-dispensed
umeclidinium (umeclidinium bromide)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide).

3. LIST OF EXCIPIENTS

Also contains lactose and magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

1 inhaler of 30 doses.
Ellipta
Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use, ONCE DAILY

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
In use shelf-life: 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/922/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

incrose ellipta

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FOIL LAMINATE TRAY LID

55 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Incruse 55 mcg inhalation powder
umeclidinium (umeclidinium bromide)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Ltd logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open until ready to inhale

In use shelf-life: 6 weeks.

7 doses

30 doses

Ellipta

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER LABEL

55 micrograms

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Incruse 55 mcg inhalation powder
umeclidinium (umeclidinium bromide)

Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

In use shelf-life: 6 weeks.

Discard by:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7 doses

30 doses

6. OTHER

Ellipta

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Incruse 55 micrograms inhalation powder, pre-dispensed umeclidinium (umeclidinium bromide)

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Incruse is and what it is used for
 2. What you need to know before you use Incruse
 3. How to use Incruse
 4. Possible side effects
 5. How to store Incruse
 6. Contents of the pack and other information
- Step-by-step instructions for use

1. What Incruse is and what it is used for

What Incruse is

Incruse contains an active substance called umeclidinium bromide, which belongs to a group of medicines called *bronchodilators*.

What Incruse is used for

This medicine is used to treat *chronic obstructive pulmonary disease (COPD)* in adults. COPD is a long-term condition in which the airways and air-sacs in the lungs gradually become blocked or damaged, leading to breathing difficulties that slowly get worse. Difficulties in breathing is added to by tightening of the muscles around the airways, which narrows the airways and so restricts the flow of air.

This medicine blocks the tightening of these muscles, making it easier for air to get in and out of the lungs. When used regularly, it can help control your breathing difficulties and reduce the effects of COPD on your everyday life.

Incruse should not be used to relieve a sudden attack of breathlessness or wheezing.

If you get this sort of attack you must use a quick-acting reliever inhaler (such as salbutamol).

2. What you need to know before you use Incruse

Do not use Incruse:

- if you are **allergic** to umeclidinium or any of the other ingredients of this medicine (*listed in section 6*).

If you think the above applies to you, **don't use** this medicine until you have checked with your doctor.

Warnings and precautions

Talk to your doctor before using this medicine:

- if you have **asthma** (Don't use Incruse to treat asthma)
- if you have **heart problems**
- if you have an eye problem called **narrow-angle glaucoma**
- if you have an **enlarged prostate, difficulty passing urine** or a **blockage in your bladder**
- if you have **severe liver problems**

Check with your doctor if you think any of these may apply to you.

Immediate breathing difficulties

If you get tightness of the chest, coughing, wheezing or breathlessness immediately after using your Incruse inhaler:

Stop using this medicine and seek medical help immediately, as you may have a serious condition called paradoxical bronchospasm.

Eye problems during treatment with Incruse

If you get eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes during treatment with Incruse:

Stop using this medicine and seek medical help immediately, these may be signs of an acute attack of narrow-angle glaucoma.

Children and adolescents

This medicine should not be given to **children or adolescents below the age of 18 years**.

Other medicines and Incruse

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor or pharmacist if you are taking other long-acting medicines similar to this medicine for breathing problems, e.g. tiotropium. You should not use Incruse as well as these other medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, **ask your doctor for advice** before using this medicine. You should not use this medicine if you are pregnant unless your doctor tells you so.

It is not known whether the ingredients of Incruse can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you use Incruse.

Driving and using machines

It is unlikely that this medicine will affect your ability to drive or use machines.

Incruse contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using this medicine.

3. How to use Incruse

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one inhalation every day at the same time of day. You only need to inhale once a day because the effect of this medicine lasts for 24 hours.

Don't use more than your doctor tells you to use.

Use Incruse regularly

It is very important that you use Incruse every day, as instructed by your doctor. This will help to keep you free of symptoms throughout the day and night.

Do **not** use this medicine to relieve a **sudden attack of breathlessness or wheezing**. If you get this sort of attack you must use a quick-acting reliever inhaler (such as salbutamol).

How to use the inhaler

See '*Step-by-step instructions for use*' in this leaflet for full information.

To use Incruse, you breathe it into your lungs through your mouth using the Ellipta inhaler.

If your symptoms do not improve

If your COPD symptoms (breathlessness, wheezing, cough) do not improve or get worse, or if you are using your quick-acting inhaler more often:

contact your doctor as soon as possible.

If you use more Incruse than you should

If you accidentally take too much of this medicine, **contact your doctor or pharmacist for advice immediately** as you may need medical attention. If possible, show them the inhaler, the package or this leaflet. You may notice that your heart is beating faster than usual, you have visual disturbances or have a dry mouth.

If you forget to use Incruse

Don't take an extra dose to make up for a missed dose. Just take your next dose at the usual time.

If you become wheezy or breathless, use your quick-acting inhaler (such as salbutamol), then seek medical advice.

If you stop using Incruse

Use this medicine for as long as your doctor recommends. It will only be effective as long as you are using it. Don't stop unless your doctor advises you to, even if you feel better, as your symptoms may get worse.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions

Allergic reactions to Incruse are uncommon (they affect less than 1 person in 100).

If you have any of the following symptoms after taking Incruse:

- itching
- skin rash (hives) or redness

Stop using Incruse and seek medical help immediately.

Common side effects

These may affect **up to 1 in 10** people:

- faster heart beat

- painful and frequent urination (may be signs of a urinary tract infection)
- common cold
- infection of nose and throat
- cough
- feeling of pressure or pain in the cheeks and forehead (may be signs of inflammation of the sinuses called sinusitis)
- headache.

Uncommon side effects

These may affect **up to 1 in 100** people:

- irregular heart beat
- constipation
- dry mouth
- rash
- taste disturbance.

Rare side effects

These may affect **up to 1 in 1,000** people:

- eye pain

Other side effects

Other side effects have occurred in a very small number of people but their exact frequency is unknown:

- Decrease in vision or pain in your eyes due to high pressure (possible signs of glaucoma).
- Blurred vision
- increase of the measured eye pressure
- Difficulty and pain when passing urine – these may be signs of a bladder obstruction or urinary retention

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Incruse

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, tray and inhaler after 'EXP'. The expiry date refers to the last day of that month.

Store in the sealed tray in order to protect from moisture and do not open the foil lid until ready for first use. Once the tray is opened, the inhaler can be used for up to 6 weeks, starting from the date of opening the tray. 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.

Do not store above 30°C.

If you store in a refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. This will help to protect the environment.

6. Contents of the pack and other information

What Incruse contains

The active substance is umeclidinium bromide.

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide).

The other ingredients are lactose monohydrate (see section 2 under 'Incruse contains lactose') and magnesium stearate.

What Incruse looks like and contents of the pack

The Ellipta inhaler itself consists of a grey plastic body, a light green mouthpiece cover and a dose counter. It is packaged in a foil laminate tray with a peelable foil lid. The tray contains a desiccant packet, to reduce moisture in the packaging.

The active substance is present as a white powder in a blister strip inside the inhaler. Each inhaler contains either 7 or 30 doses. Multipacks containing 90 (3 inhalers of 30) doses are also available. Not all pack sizes may be available in your country.

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This leaflet was last revised in

Other sources of information

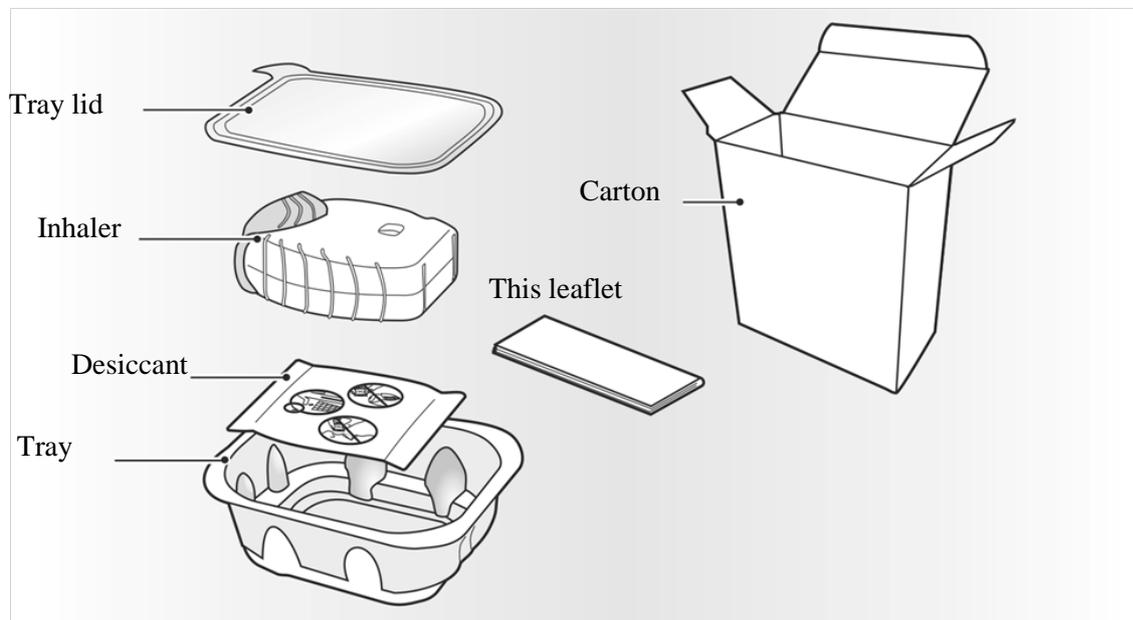
Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

Step-by-step instructions for use

What is the inhaler?

The first time you use Incruse you do not need to check that the inhaler is working properly; it contains previously measured doses and is ready to use straight away.

Your Incruse inhaler carton contains



The inhaler is packaged in a tray. **Do not open the tray until you are ready to inhale a dose of your medicine.** When you are ready to use your inhaler, peel back the lid to open the tray. The tray contains a **desiccant** sachet, to reduce moisture. Throw this desiccant sachet away – **don't** open, eat or inhale it.



When you take the inhaler out of its tray, it will be in the 'closed' position. **Don't open the inhaler until you are ready to inhale a dose of medicine.** When the tray is opened, write the "Discard by" date on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date you opened the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

The instructions for use of the inhaler provided below can be used for either the 30-dose inhaler (30 day supply) or the 7-dose inhaler (7 day supply).

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.

It is not possible to accidentally take extra medicine or a double dose in one inhalation.

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.

It counts down by **1** each time you open the cover.

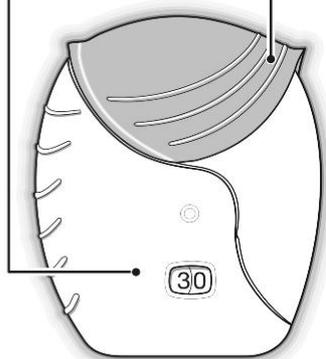
When fewer than 10 doses are left, half of the dose counter shows red.

After you have used the last dose, **half of the dose counter shows red and the number 0 is displayed.** Your inhaler is now empty.

If you open the cover after this, the dose counter will change from half red to completely red.

Cover

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

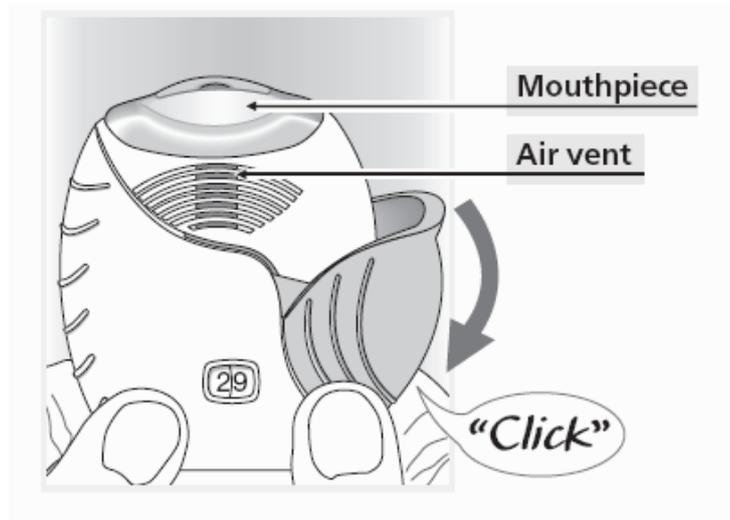


1) Prepare a dose

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

Do not shake the inhaler.

- **Slide the cover down until you hear a “click”.**



Your medicine is now ready to be inhaled.

The dose counter counts down by **1** to confirm.

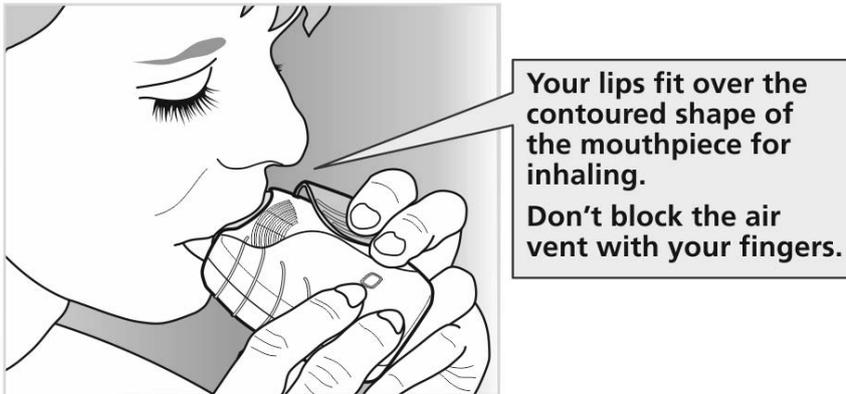
- **If the dose counter does not count down as you hear the “click”, the inhaler will not deliver medicine.**
Take it back to your pharmacist for advice.

2) Inhale your medicine

- **While holding the inhaler away from your mouth, breathe out as far as is comfortable.**

Don't breathe out into the inhaler.

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

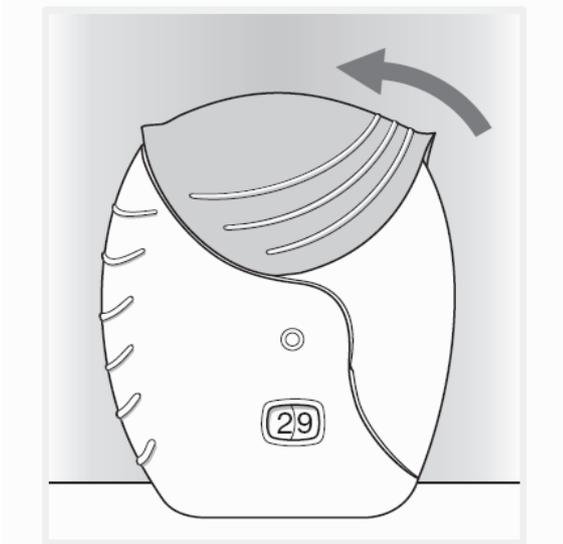


- Take one long, steady, deep breath in. Hold this breath in for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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

If you want to clean the mouthpiece, use a **dry tissue, before** you close the cover.

3) **Close the inhaler**



Slide the cover upwards as far as it will go, to cover the mouthpiece.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for umeclidinium bromide, the scientific conclusions of CHMP are as follows:

- 1 serious ADR of “ocular hypertension” with positive de-challenge and 2 non-serious “intraocular pressure increased” have been reported cumulatively with Umeclidinium bromide therapy;
- “Ocular hypertension” or “intraocular pressure increased” are known class effect of antimuscarinic that could lead to glaucoma;
- The Product information of Umeclidinium bromide/Vilanterol has been recently updated to include the undesirable effect “intraocular pressure increased”;

Based on the above, the PRAC concluded that the product information of Umeclidinium bromide should be updated to reflect the undesirable effects “intraocular pressure increased” under the SOC “eye disorders” with frequency “not known”.

Therefore, in view of the data presented in the reviewed PSUR, the PRAC considers that changes to the product information of medicinal products containing umeclidinium bromide are warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for umeclidinium bromide the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing umeclidinium bromide is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.