1. NAME OF THE MEDICINAL PRODUCT

Incruse Ellipta 55 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) 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 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 Ellipta 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

The recommended dose is one inhalation once daily.

It should be administered each day at the same time of the day to maintain bronchodilation. The maximum dose is one inhalation once daily. If a dose is missed the next dose should be inhaled at the usual time the next day.

Special populations

Elderly
No dose adjustment is required in patients 65 years of age or older (see section 5.2).

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

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. Umeclidinium 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 umeclidinium in the paediatric population (under 18 years of age) for the indication of COPD.

Method of administration

For inhalation use only.

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

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.

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 medicinal product or a double dose in one inhalation.

Instructions for use

a) Prepare a dose

Open the cover when ready to inhale 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 medicinal product 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 or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Asthma

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

Paradoxical bronchospasm

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

Deterioration of disease

Umeclidinium 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, 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 (see section 4.8). Patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.

Antimuscarinic activity

Due to its antimuscarinic activity, umeclidinium 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, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Other antimuscarinics

Co-administration of umeclidinium 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 is a substrate of cytochrome P450 2D6 (CYP2D6). The steady-state pharmacokinetics of umeclidinium 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 AUC was observed at an 8-fold higher dose with no effect on umeclidinium C_{max}. Based on the magnitude of these changes, no clinically relevant interaction is expected when umeclidinium is co-administered with CYP2D6 inhibitors or when administered to subjects genetically deficient in CYP2D6 activity (poor metabolisers).

Umeclidinium 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 was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium C_{max}. An approximately 1.4-fold increase in umeclidinium AUC was observed. Based on the magnitude of these changes, no clinically relevant interaction is expected when umeclidinium is co-administered with P-gp inhibitors.

Other medicinal products for COPD

Although no formal *in vivo* interaction studies have been performed, inhaled umeclidinium 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 or limited amount of data from the use of umeclidinium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

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

Breast-feeding

It is unknown whether umeclidinium 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 Ellipta therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

Umeclidinium 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 are nasopharyngitis (6%) and upper respiratory tract infection (5%).

Tabulated list of adverse reactions
The safety profile of umeclidinium was evaluated in patients with COPD who received doses of 55 micrograms or greater for up to one year. This includes 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 efficacy studies , the long-term safety study (which involved patients who received umeclidinium), post-marketing studies and spontaneous reporting.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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 Anaphylaxis	 Uncommon Rare
Nervous system disorders	Headache Dysgeusia Dizziness	Common Uncommon Not known
Eye disorders	Eye pain Glaucoma Vision blurred Intraocular pressure increased	Rare Not known Not known Not known
Cardiac disorders	Tachycardia Atrial fibrillation Rhythm idioventricular Supraventricular tachycardia Supraventricular extrasystoles	Common Uncommon Uncommon Uncommon Uncommon
Respiratory, thoracic and mediastinal disorders	Cough Oropharyngeal pain Dysphonia	Common Common Uncommon
Gastrointestinal disorders	Constipation Dry mouth	Common 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
(https://sideeffects.health.gov.il/).
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

An overdose of umeclidinium will likely produce signs and symptoms consistent with the known inhaled muscarinic antagonist adverse reactions (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 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 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) umeclidinium provided a clinically meaningful improvement over placebo in lung function (as measured by forced expiratory volume in 1 second [FEV_1]) 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 FEV_1 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 umeclidinium 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 and safety

The clinical efficacy of umeclidinium administered once daily was evaluated in 904 adult patients who received umeclidinium 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, umeclidinium demonstrated statistically significant and clinically meaningful improvements in lung function (as defined by change from baseline trough FEV_1 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 umeclidinium 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.

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*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.

Table 1: Trough FEV_1 (mL) at week 12 and week 24 (primary endpoint)

Treatment with umeclidinium 55 mcg	12-week study Treatment difference[1] 95% Confidence interval p-value	24-week study Treatment difference[1] 95% Confidence interval p-value
Versus Placebo	127 (52, 202) <0.001	115 (76, 155) <0.001

mcg = micrograms
[1.]least squares mean (95% confidence interval)

Umeclidinium demonstrated a statistically significant greater improvement from baseline in weighted mean FEV_1 over 0-6 hours post-dose at week 12 compared with placebo (166 mL, p<0.001) in the 12-week pivotal study. Umeclidinium demonstrated a greater improvement from baseline in weighted mean FEV_1 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 umeclidinium (1.0 units, p=0.05). A statistically significant improvement compared with placebo in the TDI focal score at week 24 was demonstrated for umeclidinium (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 umeclidinium (38%) compared with placebo (15%) in the 12-week study. Similarly, a greater proportion of patients achieved ≥1 unit TDI focal score for umeclidinium (53%) compared with placebo (41%) at week 24 in the 24-week study.

Health-related quality of life:
Umeclidinium 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 umeclidinium (-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 umeclidinium 55 micrograms (44%) compared with placebo (26%) in the 12-week study. Similarly, a greater proportion of patients achieved at least the MCID for umeclidinium at week 24 (44%) compared with placebo (34%) in the 24-week study.

COPD exacerbations
In the 24-week placebo-controlled study in patients with symptomatic COPD, umeclidinium reduced the risk of a moderate/severe COPD exacerbation by 40% compared with placebo (analysis of time to first exacerbation; Hazard Ratio 0.6; 95% CI: 0.4, 1.0, p=0.035[*]). The probability of having an exacerbation in patients receiving umeclidinium 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.
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Use of rescue medicinal product
In the 12-week study, umeclidinium 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 umeclidinium, 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 umeclidinium (Difference = -0.3; 95% CI: -0.8, 0.2, p=0.276). Patients receiving umeclidinium 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 a randomised, double-blind, 52-week study (CTT116855, IMPACT) of 10,355 adult patients with symptomatic 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 92/55/22 micrograms) once daily as a single inhaler was compared with fluticasone furoate/vilanterol (FF/VI 92/22 micrograms) once daily as a single inhaler. The primary endpoint was annual rate of on-treatment moderate and severe exacerbations in subjects treated with FF/UMC/VI compared with FF/VI. The mean annual rate of exacerbations was 0.91 and 1.07 for FF/UMEC/VI and FF/VI respectively (Rate Ratio: 0.85; 95% CI: 0.80, 0.90; p<0.001).
At week 52, a statistically significant improvement in the least-squares (LS) mean change from baseline in trough FEV1 was observed for FF/UMEC/VI compared with FF/VI (mean change: +94 mL vs. -3 mL; treatment difference: 97 mL; 95% CI: 85, 109; p<0.001).

In two 12-week, placebo controlled studies (200109 and 200110), the addition of umeclidinium 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 FEV_1 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 these two studies and limited number of exacerbation events, preclude any conclusion regarding additional effect of umeclidinium on COPD exacerbation rate.

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

5.2 Pharmacokinetic properties

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 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 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 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 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 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.

Special populations

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

Renal impairment
Subjects with severe renal impairment (creatinine clearance <30 mL/min) showed no evidence of an increase in systemic exposure to umeclidinium (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 (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.

Other special populations
A population pharmacokinetic analysis showed that no dose adjustment is required for umeclidinium 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.

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 non-clinical studies with umeclidinium, findings were those typically associated with the primary pharmacology of muscarinic receptor antagonists and/or local irritancy.

Toxicity to reproduction
Umeclidinium was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium 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

The expiry date of the product is indicated on the packaging materials.

In-use shelf-life after opening the tray: 6 weeks, but not later than the expiry date.

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, but not later than the expiry date. Do not open the tray until ready to inhale.

Write the date the inhaler should be discarded on the label and carton 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, a light green mouthpiece cover and a dose counter, packed into a foil laminate tray containing a silica gel desiccant sachet. The tray is sealed with a peelable foil lid.

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

The inhaler contains one aluminium foil laminate blister of 7 or 30 doses (7 or 30 day supply).
Pack sizes of 1 inhaler with 7 or 30 doses.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations),
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8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

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