ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LAVENTAIR ELLIPTA 55 micrograms/22 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 65 micrograms umeclidinium bromide equivalent to 55 micrograms of umeclidinium and 22 micrograms of vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate).

Excipient with known effect

Each delivered dose contains approximately 24 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 light grey inhaler (ELLIPTA) with a red mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LAVENTAIR 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 and maximum dose is one inhalation once daily.

LAVENTAIR ELLIPTA should be administered at the same time of the day each day to maintain bronchodilation. 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. The use of LAVENTAIR ELLIPTA 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 LAVENTAIR ELLIPTA 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 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 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 substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Asthma

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

Paradoxical bronchospasm

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

Not for acute use

Umeclidinium/vilanterol is not indicated for the treatment of acute episodes of bronchospasm.

Deterioration of disease

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control. In the event of deterioration of COPD during treatment with umeclidinium/vilanterol, 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 and sympathomimetics, including umeclidinium/vilanterol (see section 4.8). Patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium/vilanterol should be used with caution in patients with severe cardiovascular disease.

Antimuscarinic activity

Due to its antimuscarinic activity, umeclidinium/vilanterol should be used with caution in patients with urinary retention or with narrow-angle glaucoma.

Hypokalaemia

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

No clinically relevant effects of hypokalaemia were observed in clinical studies with umeclidinium/vilanterol at the recommended therapeutic dose. Caution should be exercised when umeclidinium/vilanterol is used with other medicinal products that also have the potential to cause hypokalaemia (see section 4.5).

Hyperglycaemia

Beta$_2$-adrenergic agonists may produce transient hyperglycemia in some patients.

No clinically relevant effects on plasma glucose were observed in clinical studies with umeclidinium/vilanterol at the recommended therapeutic dose. Upon initiation of treatment with umeclidinium/vilanterol plasma glucose should be monitored more closely in diabetic patients.

Coexisting conditions

Umeclidinium/vilanterol should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

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/vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Beta-adrenergic blockers

Beta$_2$-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists, such as vilanterol. Concurrent use of either non-selective or selective beta-adrenergic blockers should be avoided unless there are compelling reasons for their use.

Metabolic and transporter based interactions

Vilanterol is a substrate of cytochrome P450 3A4 (CYP3A4). Concomitant administration of strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir, telithromycin) may inhibit the metabolism of, and increase the systemic exposure to, vilanterol. Co-administration with ketoconazole (400 mg) in healthy volunteers increased mean vilanterol $AUC_{(0\text{-}t)}$ and $C_{max,}$ 65% and 22% respectively. The increase in vilanterol exposure was not associated with an increase in beta-adrenergic agonist related systemic effects on heart rate, blood potassium or QT interval (corrected using the Fridericia method). Care is advised when co-administering umeclidinium/vilanterol with ketoconazole and other known strong CYP3A4 inhibitors as there is potential for an increased systemic exposure to vilanterol, which could lead to an increase in the potential for adverse reactions. Verapamil, a moderate CYP3A4 inhibitor, did not significantly affect the pharmacokinetics of vilanterol.

Umeclidinium is a substrate of cytochrome P450 2D6 (CYP2D6). The steady-state pharmacokinetics of umeclidinium was assessed in healthy volunteers lacking CYP2D6 (poor metabolisers). No effect on umeclidinium AUC or C_{max} was observed at a 8-fold higher dose. An approximately 1.3-fold increase in umeclidinium AUC was observed at 16-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/vilanterol is co-administered with CYP2D6 inhibitors or when administered to patients genetically deficient in CYP2D6 activity (poor metabolisers).

Both umeclidinium and vilanterol are substrates of the P-glycoprotein transporter (P-gp). The effect of the moderate P-gp inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy volunteers. No effect of verapamil was observed on

umeclidinium or vilanterol C_{max}. An approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when umeclidinium/vilanterol is co-administered with P-gp inhibitors.

Other antimuscarinics and sympathomimetics

Co-administration of umeclidinium/vilanterol with other long-acting muscarinic antagonists, long-acting $beta_2$-adrenergic agonists or medicinal products containing either of these agents has not been studied and is not recommended as it may potentiate known inhaled muscarinic antagonist or $beta_2$-adrenergic agonist adverse reactions (see sections 4.4 and 4.9).

Hypokalaemia

Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists, therefore use with caution (see section 4.4).

Other medicinal products for COPD

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of umeclidinium/vilanterol in pregnant women. Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant after administration of vilanterol (see section 5.3).

Umeclidinium/vilanterol 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 or vilanterol are excreted in human milk. However, other $beta_2$-adrenergic agonists are detected in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue umeclidinium/vilanterol 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/vilanterol on human fertility. Animal studies indicate no effects of umeclidinium or vilanterol on fertility.

4.7 Effects on ability to drive and use machines

Umeclidinium/vilanterol 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 reaction is nasopharyngitis (9%).

Tabulated list of adverse reactions

The safety profile of LAVENTAIR ELLIPTA is based on safety experience with umeclidinium/vilanterol and the individual components from the clinical development program comprising of 6 855 patients with COPD and from spontaneous reporting. The clinical development programme included 2 354 patients who received umeclidinium/vilanterol once daily in the Phase III clinical studies of 24 weeks or more, of whom 1 296 patients received the recommended dose of 55/22 micrograms in 24-week studies, 832 patients received a higher dose of 113/22 micrograms in 24-week studies and 226 patients received 113/22 micrograms in a 12-month study.

The frequencies assigned to the adverse reactions identified in the table below include crude incidence rates observed in the integration of five 24-week studies and in the 12-month safety study.

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	Urinary tract infection Sinusitis Nasopharyngitis Pharyngitis Upper respiratory tract infection	Common Common Common Common Common
Immune system disorders	Hypersensitivity reactions including: Rash Anaphylaxis, angioedema, and urticaria	 Uncommon Rare
Nervous system disorders	Headache Tremor Dysgeusia Dizziness	Common Uncommon Uncommon Not known
Eye disorders	Vision blurred Glaucoma Intraocular pressure increased Eye pain	Rare Rare Rare Rare
Cardiac disorders	Atrial fibrillation Supraventricular tachycardia Rhythm idioventricular Tachycardia Supraventricular extrasystoles Palpitations	Uncommon Uncommon Uncommon Uncommon Uncommon Uncommon
Respiratory, thoracic and mediastinal disorders	Cough Oropharyngeal pain Dysphonia Paradoxical bronchospasm	Common Common Uncommon Rare
Gastrointestinal disorders	Constipation Dry mouth	Common Common
Musculoskeletal and connective tissue disorders	Muscle spasms	Uncommon
Renal and urinary disorders	Urinary retention Dysuria Bladder outlet obstruction	Rare Rare Rare

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/vilanterol will likely produce signs and symptoms due to the individual components' actions, consistent with the known inhaled muscarinic antagonist adverse reactions (e.g. dry mouth, visual accommodation disturbances and tachycardia) or those with overdose of other beta$_2$-adrenergic agonists (e.g. arrhythmias, tremor, headache, palpitations, nausea, hyperglycaemia and hypokalaemia).

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, adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids, ATC code: R03AL03

Mechanism of action

Umeclidinium/vilanterol is a combination inhaled long-acting muscarinic receptor antagonist/long-acting beta$_2$-adrenergic agonist (LAMA/LABA). Following oral inhalation both compounds act locally on airways to produce bronchodilation by separate mechanisms.

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

Vilanterol
Vilanterol is a selective long-acting, beta$_2$-adrenergic receptor agonist (LABA).
The pharmacologic effects of beta$_2$-adrenergic agonists, including vilanterol, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Pharmacodynamic effects

In Phase III, 6-month studies umeclidinium/vilanterol provided clinically meaningful improvements over placebo in lung function (as measured by forced expiratory volume in 1 second [FEV_1]) over 24 hours following once daily administration, which were evident at 15 minutes following administration of the first dose (improvement over placebo by 112 ml ($p < 0.001^*$). Mean peak improvements in FEV_1 within the first 6 hours following dosing relative to placebo was 224 ml ($p<0.001^*$) at week 24. There was no evidence for tachyphylaxis in the effect of LAVENTAIR ELLIPTA over time.

Cardiac electrophysiology
The effect of umeclidinium/vilanterol on the QT interval was evaluated in a placebo and active (moxifloxacin) controlled QT study involving once daily administration of umeclidinium/vilanterol 113/22 micrograms or 500/100 micrograms (pre-dispensed dose with umeclidinium at eight times the recommended dose and vilanterol at four times the recommended dose) for 10 days in 103 healthy volunteers. The maximum mean difference in prolongations of QT interval (corrected using the Fridericia method, QT_cF) from placebo after baseline-correction was 4.3 (90% CI=2.2 to 6.4) milliseconds seen 10 minutes after administration with umeclidinium/vilanterol 113/22 micrograms and 8.2 (90% CI=6.2 to 10.2) milliseconds seen 30 minutes after administration with umeclidinium/vilanterol 500/100 micrograms. Therefore, no clinically relevant pro-arrhythmic potential related to QT-interval prolongations was observed with umeclidinium/vilanterol 113/22 micrograms.

A dose-dependent increase in heart rate was also observed. The maximum mean difference in heart rate from placebo after baseline-correction was 8.4 (90% CI=7.0 to 9.8) beats/minute and 20.3 (90% CI=18.9 to 21.7) beats/minute seen 10 minutes after administration of umeclidinium/vilanterol 113/22 micrograms and 500/100 micrograms respectively.

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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.

In addition, no clinically significant effects on cardiac rhythm were observed on 24-hour Holter monitoring in 53 patients with COPD who were treated with umeclidinium/vilanterol 55/22 micrograms once daily in one 6-month study, or in a further 55 patients who received umeclidinium/vilanterol 113/22 micrograms once daily in another 6-month study and 226 patients who received 113/22 micrograms once daily in the 12-month study.

Clinical efficacy and safety

The clinical efficacy of umeclidinium/vilanterol administered once daily was evaluated in eight Phase III clinical studies in 6 835 adult patients with a clinical diagnosis of COPD; 5 618 patients from five 6-month studies (two placebo-controlled and three active [tiotropium]-comparator controlled), 655 patients from two 3-month exercise endurance/lung function studies and 562 patients from a 12-month supportive study.

Effects on lung function
LAVENTAIR ELLIPTA demonstrated improvements in lung function (as defined by change from baseline in trough FEV_1) in several studies. In one 6-month Phase III study, LAVENTAIR ELLIPTA demonstrated statistically significant improvements in trough FEV_1 (primary endpoint) at week 24 compared with placebo and each monotherapy component treatment arm. In addition, LAVENTAIR ELLIPTA demonstrated clinically meaningful and statistically significant improvements in trough FEV_1 compared with tiotropium in two of the three 6-month active-comparator studies and numerically-greater improvements from tiotropium in the third active-comparator study (see Table 1). There was no attenuation of the bronchodilator effect over time.

Symptomatic outcomes
Breathlessness:
LAVENTAIR ELLIPTA demonstrated a statistically significant and clinically meaningful reduction in breathlessness as evaluated by an increase in TDI focal score at week 24 (key secondary end-point) compared with placebo (see Table 1). Improvements in TDI focal score compared with each monotherapy component and tiotropium were not statistically significant (see Table 1).

The proportion of patients who responded with at least the minimum clinically important difference (MCID) of 1 unit TDI focal score at week 24 was greater for LAVENTAIR ELLIPTA (58%) compared with placebo (41%) and each monotherapy component (53% for umeclidinium and 51% for vilanterol).

Health-related quality of life:
LAVENTAIR ELLIPTA has also shown an 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 24 compared with placebo and each monotherapy component (see Table 1). LAVENTAIR ELLIPTA showed a statistically significant reduction in SGRQ total score compared with tiotropium in one of the three active-comparator studies (see Table 1).

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 24 was greater for LAVENTAIR ELLIPTA (49%) compared with placebo (34%) and each monotherapy component (44% for umeclidinium and 48% for vilanterol). In one active-comparator study, a higher percentage of patients receiving LAVENTAIR ELLIPTA responded with a clinically meaningful improvement in SGRQ score at week 24 (53%) compared to tiotropium (46%). In the other two active-comparator studies, a similar proportion of patients achieved at least the MCID with LAVENTAIR ELLIPTA and tiotropium; 49% and 54% for LAVENTAIR ELLIPTA 55/22 micrograms and 52% and 55% for tiotropium.

Use of rescue medication
LAVENTAIR ELLIPTA reduced the use of rescue medication with salbutamol over weeks 1-24 compared with placebo and umeclidinium (see Table 1) and demonstrated an increase from baseline in the proportion of days when no rescue medication was needed (on average 11.1%) compared with a decrease from baseline on placebo (on average 0.9%).

In the three 6-month active-comparator-controlled studies, LAVENTAIR ELLIPTA reduced the use of rescue medication with salbutamol compared with tiotropium, with statistically significant reductions observed in two of the studies (see Table 1). LAVENTAIR ELLIPTA also demonstrated a greater increase from baseline in the proportion of days when no rescue medication was needed in all three studies (average within the range 17.6% to 21.5%) compared with tiotropium (average within the range 11.7% to 13.4%).

Table 1. Lung function, symptomatic and health related quality of life outcomes at week 24

Treatment comparisons with LAVENTAIR ELLIPTA 55/22 mcg	**Treatment difference[1] (95% confidence intervals, p-value)**			
	Trough FEV_1 (ml)	**TDI Focal Score**	**SGRQ Total Score**	**Use of rescue medication[3]**
LAVENTAIR ELLIPTA (N = 413) versus Placebo (N = 280)	167 (128, 207) <0.001	1.2 (0.7,1.7) <0.001	-5.51 (-7.88, -3.13) <0.001*	-0.8 (-1.3,-0.3) 0.001*
LAVENTAIR ELLIPTA (N = 413) versus Umeclidinium 55 mcg (N = 418)	52 (17, 87) 0.004	0.3 (-0.2, 0.7) 0.244	-0.82 (-2.90, 1.27) 0.441	-0.6 (-1.0, -0.1) 0.014*
LAVENTAIR ELLIPTA (N = 413) versus Vilanterol 22 mcg (N = 421)	95 (60, 130) <0.001	0.4 (-0.1, 0.8) 0.117	-0.32 (-2.41, 1.78) 0.767	0.1 (-0.3, 0.5) 0.675
LAVENTAIR ELLIPTA (N = 454) versus tiotropium 18 mcg (N = 451) (Study ZEP117115)	112 (81, 144) <0.001	n/e	-2.10 (-3.61, -0.59) 0.006	-0.5 (-0.7, -0.2) <0.001
LAVENTAIR ELLIPTA (N = 207) versus tiotropium 18 mcg (N = 203) (Study DB2113360)	90 (39, 141) <0.001	0.1[2] (-0.4, 0.5) 0.817	0.75 (-2.12, 3.63) 0.607	-0.7 (-1.2, -0.1) 0.022
LAVENTAIR ELLIPTA (N = 217) versus tiotropium 18 mcg (N = 215) (Study DB2113374)	60 (10, 109) 0.018*		-0.17 (-2.85, 2.52) 0.904	-0.6 (-1.2, 0.0) 0.069

N=number in Intent-to-treat population
mcg = micrograms
n/e = not evaluated

1. Least squares mean
2. Pooled data from Study DB2113360 and Study DB2113374
3. Difference in the mean number of puffs per day over weeks 1-24

* 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 higher dose of umeclidinium/vilanterol (113/22 micrograms) was also studied in a 24-week placebo controlled clinical study and in two of the three 24-week active-controlled studies. The results were similar to those for the LAVENTAIR ELLIPTA dose and provided additional supportive evidence for the efficacy of LAVENTAIR ELLIPTA.

COPD exacerbations
In a 24-week placebo-controlled study in patients with symptomatic COPD, LAVENTAIR ELLIPTA reduced the risk of a moderate/severe COPD exacerbation by 50% compared with placebo (based on analysis of time to first exacerbation: Hazard Ratio (HR) 0.5; 95% CI: 0.3, 0.8; p=0.004[*]); by 20% compared with umeclidinium (HR 0.8; 95% CI: 0.5, 1.3; p=0.391); and by 30% compared with vilanterol (HR 0.7; 95% CI: 0.4, 1.1; p=0.121). From the three active-comparator studies in patients with symptomatic COPD, the risk of a moderate/severe COPD exacerbation compared with tiotropium was reduced by 50% in one study (HR 0.5; 95% CI: 0.3, 1.0; p=0.044). In the other two studies, the risk of a moderate/severe COPD exacerbation was increased by 20% and 90% (HR 1.2; 95% CI: 0.5, 2.6; p=0.709 and HR 1.9; 95% CI: 1.0, 3.6; p=0.062 respectively). 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.

Supporting efficacy studies
In a randomised, double-blind, 52-week study (CTT116855, IMPACT), 10 355 adult patients with symptomatic COPD and a history of 1 or more moderate/severe exacerbations in the prior 12 months were randomised (1:2:2) to receive umeclidinium/vilanterol (UMEC/VI 55/22 micrograms), fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 92/55/22 micrograms), or fluticasone furoate/vilanterol (FF/VI 92/22 micrograms) administered 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 FF/VI and UMEC/VI. The mean annual rate of exacerbations was 0.91, 1.07 and 1.21 for FF/UMEC/VI, FF/VI, and UMEC/VI respectively.

The comparison of FF/UMEC/VI to FF/VI and UMEC/VI resulted in a statistically significant 14.8% reduction in risk of a moderate/severe exacerbation (based on analysis of time to first exacerbation) (Hazard Ratio 0.85; 95% CI: 0.80, 0.91; p<0.001) and 16.0% reduction in risk of a moderate/severe exacerbation respectively (based on analysis of time to first exacerbation) (Hazard Ratio 0.84; 95% CI: 0.78, 0.91; p<0.001).

Exercise endurance and lung volumes
LAVENTAIR ELLIPTA 55/22 micrograms improved exercise endurance time compared with placebo, as evaluated with the endurance shuttle walk test (ESWT), in one study but not the second and improved lung volume measures compared with placebo in both studies in adult COPD patients with hyperinflation (functional residual capacity [FRC] >120%). In the first study, LAVENTAIR ELLIPTA 55/22 micrograms demonstrated a statistically significant and clinically relevant improvement (based on a minimal clinically important difference (MCID) between 45 to 85 seconds) over placebo in exercise endurance time (EET) obtained 3 hours after dosing at week 12 (69.4 seconds [p=0.003]). Improvement in EET compared with placebo was seen at Day 2 and was sustained at week 6 and week 12. In the second study, the treatment difference in EET between LAVENTAIR ELLIPTA 55/22 micrograms and placebo was 21.9 seconds (p=0.234) at week 12.

LAVENTAIR ELLIPTA 55/22 micrograms also showed statistically significant improvements compared with placebo in change from baseline in lung volume measures at trough and at 3 hours post dose at week 12 in the first study (inspiratory capacity: 237 ml and 316 ml respectively, residual volume: -466 ml and -643 ml respectively and functional residual capacity: -351 ml and -522 ml respectively; all p<0.001). In the second study, LAVENTAIR ELLIPTA 55/22 micrograms showed improvements compared with placebo in change from baseline in lung volume measures at trough and at 3 hours post dose at week 12 (inspiratory capacity: 198 ml and 238 ml respectively, residual volume: -295 ml and -351 ml respectively and functional residual capacity: -238 ml and -302 ml respectively); all p<0.001[*]).

[*] 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.

Paediatric population

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

5.2 Pharmacokinetic properties

When umeclidinium and vilanterol were administered in combination by the inhaled route, the pharmacokinetics of each component was similar to those observed when each active substance was administered separately. For pharmacokinetic purposes each component can therefore be considered separately.

Absorption

Umeclidinium
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.

Vilanterol
Following inhaled administration of vilanterol in healthy volunteers, C_{max} occurred at 5 to 15 minutes. The absolute bioavailability of inhaled vilanterol was 27%, with negligible contribution from oral absorption. Following repeat dosing of inhaled vilanterol, steady state was achieved within 6 days with up to 2.4-fold accumulation.

Distribution

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

Vilanterol
Following intravenous administration to healthy volunteers, the mean volume of distribution at steady state was 165 litres. Vilanterol has a low association with red blood cells. *In vitro* plasma protein binding in human plasma was on average 94%.

Biotransformation

Umeclidinium
In vitro studies showed that umeclidinium is primarily 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.

Vilanterol
In vitro studies showed that vilanterol is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic routes for vilanterol are O-dealkylation to a range of metabolites with significantly reduced $beta_1$- and $beta_2$-adrenergic agonist activity. Plasma metabolic profiles following oral administration of vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low.

Elimination

Umeclidinium
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 volunteers, 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 in healthy volunteers, with 3% to 4% excreted unchanged in urine at steady-state.

Vilanterol
Plasma clearance of vilanterol following intravenous administration was 108 litres/hour. Following oral administration of radiolabelled vilanterol, mass balance showed 70% of the radiolabel in urine and 30% in faeces. Primary elimination of vilanterol was by metabolism followed by excretion of metabolites in urine and faeces. Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours.

Special populations

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

Renal impairment
Patients with severe renal impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC) following administration of umeclidinium/vilanterol with umeclidinium at twice the recommended dose and vilanterol at the recommended dose and no evidence of altered protein binding between patients with severe renal impairment and healthy volunteers.

Hepatic impairment
Patients with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC) following administration of umeclidinium/vilanterol with umeclidinium at twice the recommended dose and vilanterol at the recommended dose and no evidence of altered protein binding between patients with moderate hepatic impairment and healthy volunteers. Umeclidinium/vilanterol has not been evaluated in patients with severe hepatic impairment.

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

In non-clinical studies with umeclidinium and vilanterol, alone and in combination, findings were those typically associated with the primary pharmacology of either muscarinic receptor antagonists or $beta_2$-adrenergic agonists respectively and/or local irritancy. The following statements reflect studies conducted on the individual components.

Genotoxicity and carcinogenicity

Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 26 or ≥ 22-fold, times the human clinical exposure of umeclidinium 55 micrograms, based on AUC, respectively.

In genetic toxicity studies, vilanterol (as alpha-phenylcinnamate) and triphenylacetic acid were not genotoxic indicating that vilanterol (as trifenatate) does not represent a genotoxic hazard to humans. Consistent with findings for other beta$_2$-adrenergic agonists, in lifetime inhalation studies, vilanterol trifenatate caused proliferative effects in the female rat and mouse reproductive tract and in the rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 0.5- or 13-fold, times the human clinical exposure of vilanterol 22 micrograms based on AUC, respectively.

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).

Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, vilanterol caused effects similar to those seen with other beta$_2$-adrenergic agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation) at 6-times the human clinical exposure based on AUC. When given subcutaneously there were no effects at 36-times the human clinical exposure of vilanterol 22 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 a 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.

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 light grey body, red 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 two aluminium foil laminate blisters of 7 or 30 doses.

Pack sizes of 1 inhaler with 7 or 30 doses. Multipacks containing 90 (3 inhalers of 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. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/899/001
EU/1/14/899/002
EU/1/14/899/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 May 2014
Date of latest renewal: 11 January 2019

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 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 RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Glaxo Wellcome Production
Zone Industrielle No.2
23 Rue Lavoisier
27000 Evreux
France

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 (PSURs)**

The requirements for submission of PSURs 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (SINGLE PACKS)

1. NAME OF THE MEDICINAL PRODUCT

LAVENTAIR ELLIPTA 55 micrograms/22 micrograms inhalation powder, pre-dispensed
umeclidinium/vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate).

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed.
1 inhaler of 7 doses
1 inhaler of 30 doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily
Read the package leaflet before use.
Inhalation use
Do not shake.

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

Do not swallow the desiccant.

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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland
GlaxoSmithKline (Ireland) Limited logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/899/001 1 inhaler of 7 doses
EU/1/14/899/002 1 inhaler of 30 doses

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

laventair 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

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

LAVENTAIR ELLIPTA 55 micrograms/22 micrograms inhalation powder, pre-dispensed
umeclidinium/vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate).

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed.
Multipack: 90 (3 inhalers of 30) doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily
Read the package leaflet before use.
Inhalation use
Do not shake.

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

Do not swallow the desiccant.

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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland
GlaxoSmithKline (Ireland) Limited logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/899/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

laventair 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 CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

LAVENTAIR ELLIPTA 55 micrograms/22 micrograms inhalation powder, pre-dispensed
umeclidinium/vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate).

3. LIST OF EXCIPIENTS

Excipients: lactose monohydrate and magnesium stearate
See package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed
1 inhaler of 30 doses
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Once daily
Read the package leaflet before use.
Inhalation use
Do not shake.

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

Do not swallow the desiccant.

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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland
GlaxoSmithKline (Ireland) Limited logo

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/899/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

laventair ellipta

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

FOIL LAMINATE TRAY LID

1. NAME OF THE MEDICINAL PRODUCT

LAVENTAIR ELLIPTA 55/22 mcg inhalation powder
umeclidinium/vilanterol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited logo
GlaxoSmithKline (Ireland) Limited

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

INHALER LABEL

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

LAVENTAIR ELLIPTA 55/22 mcg inhalation powder
umeclidinium/vilanterol
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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

LAVENTAIR ELLIPTA 55 micrograms/22 micrograms inhalation powder, pre-dispensed

umeclidinium/vilanterol

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 LAVENTAIR ELLIPTA is and what it is used for

What LAVENTAIR ELLIPTA is

LAVENTAIR ELLIPTA contains two active substances umeclidinium bromide and vilanterol. These belong to a group of medicines called bronchodilators.

What LAVENTAIR ELLIPTA is used for

LAVENTAIR ELLIPTA is used to treat chronic obstructive pulmonary disease (**COPD**) in adults. COPD is a long-term condition characterised by breathing difficulties that slowly get worse.

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

LAVENTAIR ELLIPTA 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). If you do not have a quick-acting inhaler contact your doctor.

2. What you need to know before you use LAVENTAIR ELLIPTA

Do not use LAVENTAIR ELLIPTA:
- if you are **allergic** to umeclidinium, vilanterol or any of the other ingredients of this medicine (listed in section 6).

If you think this applies to you, **do not 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** (Do not use LAVENTAIR ELLIPTA to treat asthma)
- if you have **heart problems** or **high blood pressure**
- 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 suffer from **epilepsy**
- if you have **thyroid gland problems**
- if you have **low potassium** in your blood
- if you have **diabetes**
- 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 LAVENTAIR ELLIPTA 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 LAVENTAIR ELLIPTA
If you get eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in association with red eyes during treatment with LAVENTAIR ELLIPTA:

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

Children and adolescents
Do not give this medicine to **children or adolescents below the age of 18 years**.

Other medicines and LAVENTAIR ELLIPTA
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. If you are not sure what your medicine contains talk to your doctor or pharmacist.

Some medicines may affect how this medicine works, or make it more likely that you'll have side effects. These include:

- medicines called beta blockers (such as propranolol), to treat **high blood pressure** or other **heart problems**
- ketoconazole or itraconazole, to treat **fungal infections**
- clarithromycin or telithromycin, to treat **bacterial infections**
- ritonavir, to treat **HIV infection**
- medicines that lower the amount of potassium in your blood, such as some diuretics (water tablets) or some medicines used to treat asthma (such as methylxanthine or steroids)
- other long-acting medicines similar to this medicine that are used to treat breathing problems, e.g. tiotropium, indacaterol. Do not use LAVENTAIR ELLIPTA if you already use these medicines.

Tell your doctor or pharmacist if you are taking any of these. Your doctor may wish to monitor you carefully if you are taking any of these medicines as they may increase the side effects of LAVENTAIR ELLIPTA.

Pregnancy and breast-feeding
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. Do not use this medicine if you are pregnant unless your doctor tells you that you can.

It is not known whether the ingredients of LAVENTAIR ELLIPTA can pass into breast milk. **If you are breast-feeding, you must check with your doctor** before you use LAVENTAIR ELLIPTA. Do not use this medicine if you are breast-feeding unless your doctor tells you that you can.

Driving and using machines
It is unlikely that LAVENTAIR ELLIPTA will affect your ability to drive or use machines.

LAVENTAIR ELLIPTA 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 LAVENTAIR ELLIPTA

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.
Do not use more than your doctor tells you to use.

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

LAVENTAIR ELLIPTA 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).

How to use the inhaler
See 'Step-by-step instructions' at the end of this leaflet for full information.

LAVENTAIR ELLIPTA is for inhalation use. To use LAVENTAIR ELLIPTA, 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 LAVENTAIR ELLIPTA than you should
If you accidentally use 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 feel shaky, you have visual disturbances, have a dry mouth, or have a headache.

If you forget to use LAVENTAIR ELLIPTA
Do not inhale an extra dose to make up for a forgotten dose. Just inhale your next dose at the usual time. If you become wheezy or breathless, use your quick-acting reliever inhaler (such as salbutamol), then seek medical advice.

If you stop using LAVENTAIR ELLIPTA
Use this medicine for as long as your doctor recommends. It will only be effective as long as you are using it. Do not 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
If you have any of the following symptoms after taking LAVENTAIR ELLIPTA **stop using this medicine and tell your doctor immediately**.

Uncommon side effects (may affect up to 1 in 100 people):
- skin rash (hives) or redness

Rare side effects (may affect up to 1 in 1 000 people):
- swelling, sometimes of the face or mouth (angioedema)
- becoming very wheezy, coughing or having difficulty in breathing
- suddenly feeling weak or light headed (which may lead to collapse or loss of consciousness)

Immediate breathing difficulties
Immediate breathing difficulties after using LAVENTAIR ELLIPTA are rare. If you get tightness of the chest, coughing, wheezing or breathlessness immediately after using this medicine:
stop using this medicine and seek medical help immediately, as you may have a serious condition called paradoxical bronchospasm.

Other side effects

Common (may affect up to 1 in 10 people)
- painful and frequent urination (may be signs of a urinary tract infection)
- combination of sore throat and runny nose
- sore throat
- feeling of pressure or pain in the cheeks and forehead (may be signs of inflammation of the sinuses called sinusitis)
- headache
- cough
- pain and irritation in the back of the mouth and throat
- constipation
- dry mouth
- infection of the upper airways.

Uncommon (may affect up to 1 in 100 people)
- irregular heart beat
- faster heart beat
- awareness of heart beat *(palpitations)*
- muscle spasms
- tremor
- taste disturbance
- hoarseness.

Rare (may affect up to 1 in 1 000 people)
- blurred vision
- increase of the measured eye pressure
- decrease in vision or pain in your eyes (possible signs of glaucoma)
- difficulty and pain when passing urine – these may be signs of a bladder obstruction or urinary retention.

Not known (frequency cannot be estimated from the available data)
- dizziness.

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 LAVENTAIR ELLIPTA

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.

Keep the inhaler inside the sealed tray in order to protect from moisture and only remove immediately before 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 thrown away 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 stored 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 throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What LAVENTAIR ELLIPTA contains
The active substances are umeclidinium bromide and vilanterol.

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 55 micrograms umeclidinium (equivalent to 65 micrograms of umeclidinium bromide) and 22 micrograms of vilanterol (as trifenatate).

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

What LAVENTAIR ELLIPTA looks like and contents of the pack
LAVENTAIR ELLIPTA is an inhalation powder, pre-dispensed.
The Ellipta inhaler consists of a light grey plastic body, a red 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 substances are present as a white powder in separate blisters inside the inhaler.

LAVENTAIR ELLIPTA is available in packs of 1 inhaler containing either 7 or 30 doses and in multipacks containing 90 (3 inhalers of 30) doses. Not all pack sizes may be marketed.

Marketing Authorisation Holder:

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Manufacturer:

Glaxo Wellcome Production
Zone Industrielle No.2
23 Rue Lavoisier
27000 Evreux
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
GlaxoSmithKline Pharmaceuticals s.a./n.v.
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This leaflet was last revised in

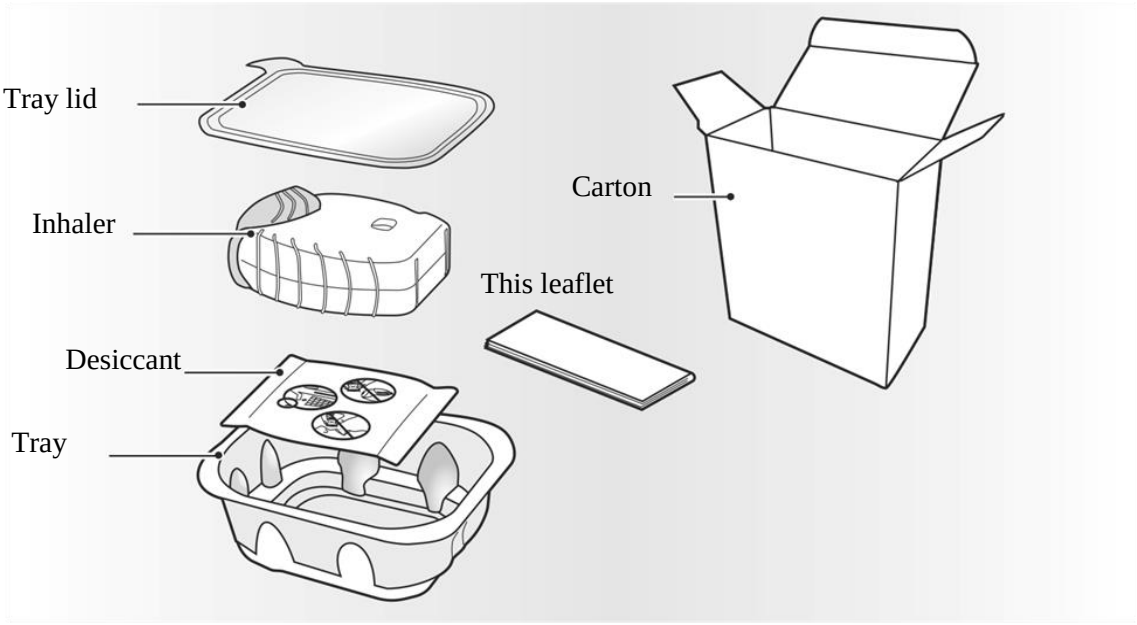
Other sources of information

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

Step-by-step instructions

What is the ELLIPTA inhaler?
The first time you use LAVENTAIR ELLIPTA 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 LAVENTAIR ELLIPTA inhaler carton contains



The inhaler is packaged in a tray. **Do not open the tray until you are ready to start using your new inhaler**. 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 – **do not** open, eat or inhale it.

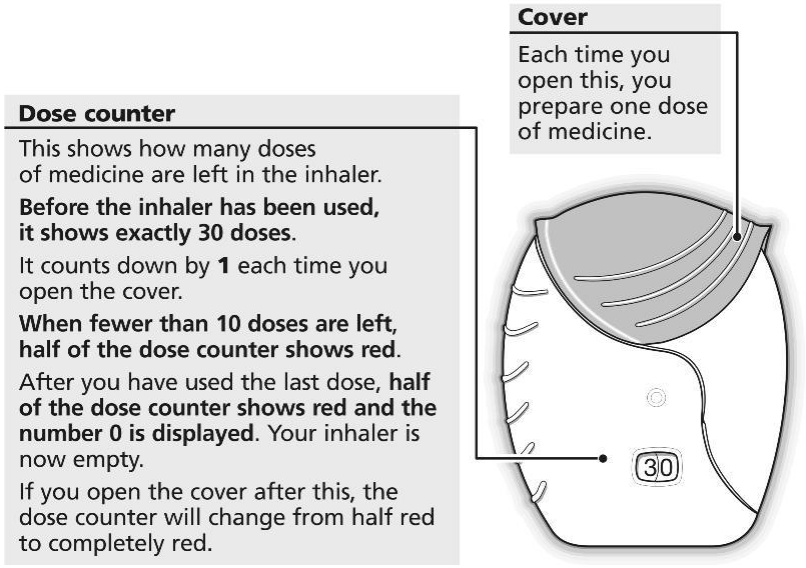
When you take the inhaler out of its tray, it will be in the 'closed' position. **Do not open the inhaler until you are ready to inhale a dose of medicine**. When the tray is opened, write the "Discard by" date on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date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

If stored in a refrigerator, allow the inhaler to return to room temperature for at least one hour before use.

The step-by-step 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).

1) Read this before you start

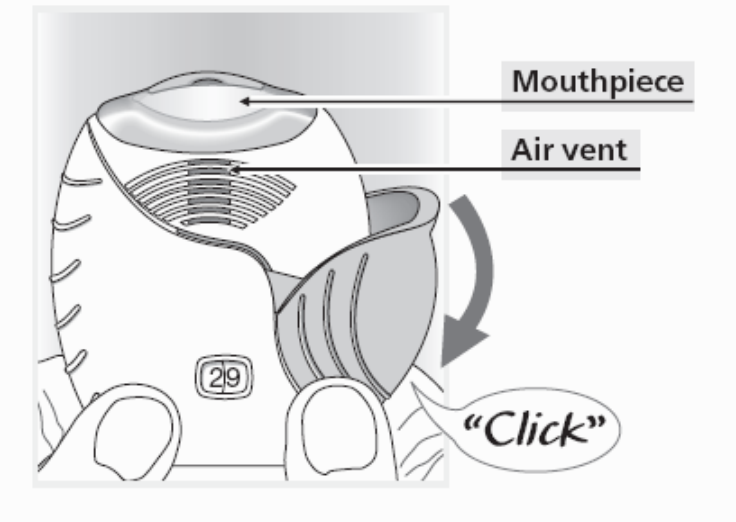
If you open and close the cover without inhaling the medicine, you will lose the dose.
The lost dose will be securely held inside the inhaler, but it will no longer be available.
It is not possible to accidentally take extra medicine or a double dose in one inhalation.



2) Prepare a dose

Wait to open the cover until you are ready to inhale your dose.
Do not shake the inhaler.

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



Your medicine is now ready to be inhaled.

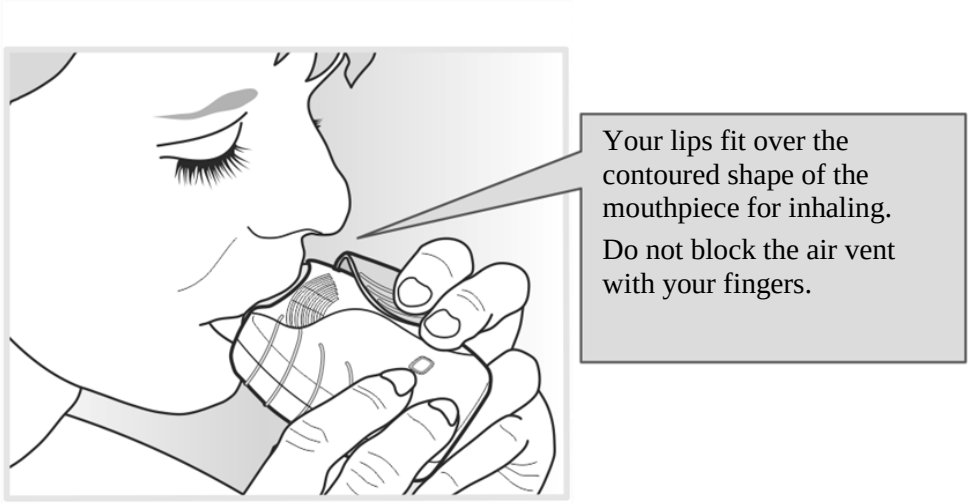
The dose counter counts down by **1** to confirm.

- **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.

3) Inhale your medicine

- **While holding the inhaler away from your mouth, breathe out as far as is comfortable.**
  Do not breathe out into the inhaler.

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

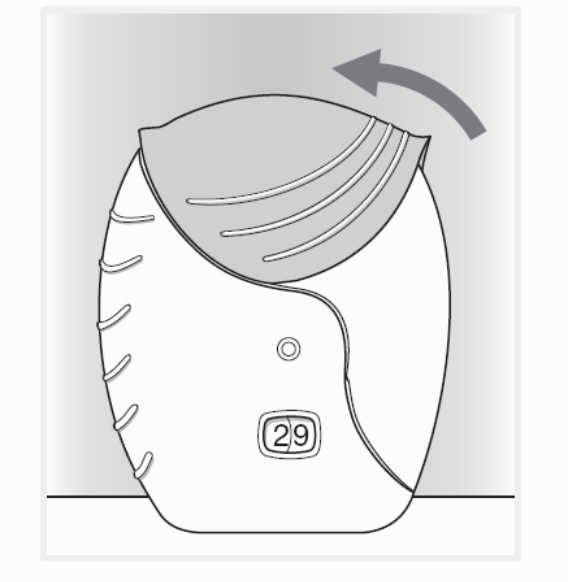


- Take one long, steady, deep breath in. Hold this breath in for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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.

4) 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 for the non-interventional imposed PASS final study report for the medicinal products mentioned above, the scientific conclusions of CHMP are as follows:

Rolufta Ellipta, Incruse Ellipta, Anoro Ellipta and Laventair Ellipta (umeclidinium bromide, umeclidinium bromide/vilanterol) are removed from the additional monitoring list as the condition to the marketing authorisation has been fulfilled. This relates to the conduction of a Post-authorisation Safety Observational Cohort Study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events (MI, stroke, heart failure or sudden cardiac death) in COPD patients using inhaled UMEC/VI combination or inhaled UMEC versus Tiotropium (Study 201038) which was imposed as a condition to the Marketing Authorisation (category 1 PASS), due to concerns on cardiovascular and cerebrovascular safety. According to the protocol, the HR (95% CI) were calculated for each treatment comparison; the non-inferiority criterion was the upper bound of the 95% confidence interval (CI) around the hazard ratio not exceeding 2.0 and the lower bound of the 95% CI not exceeding 1.0. Other secondary safety endpoints were studied. Effectiveness outcomes were also evaluated, such as persistence with study medication, frequency of exacerbations.

The adjusted HR (95% CI) for the composite outcome was 1.254 (0.830, 1.896) for UMEC vs. TIO cohorts, and 1.352 (0.952, 1.922) for UMEC/VI vs. TIO. The adjusted HR of UMEC/VI vs TIO is not statistically significant, but close to the established limits. An increased risk of MI was observed in UMEC/VI cohort with respect to tiotropium: adjusted HR of 2.195 (1.053, 4.575). The risk of MI was lower between the UMEC and TIO (adjusted HR (95% CI) of 1.754 (0.748, 4.115)). It is acknowledged that the study was powered to test for differences between cohorts for the primary composite endpoint only and not to test for non-inferiority in the secondary endpoints; however, such difference in the MI risk is to be noted.

COPD, Pneumonia and Lower respiratory tract infection were the most frequently reported events in patients who had received UMEC/VI for longer than one year. The majority of the serious events were attributed to exacerbation complicating advanced stage COPD in most of the cases; excluding a potential relationship with the treatment UMEC/VI.

In conclusion, the PRAC considered that the benefit-risk balance of the concerned medicinal products remained unchanged.

This PASS study was a condition of the marketing authorisations of medicinal products containing the active substance umeclidinium bromide, umeclidinium bromide/vilanterol. This condition is now considered fulfilled and consequently an update of the Annex II conditions or restrictions with regard to the safe and effective use of the medicinal product is recommended to remove this condition, as well as deletion of additional monitoring statements in Annexes I and IIIB.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

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

On the basis of the scientific conclusions for umeclidinium bromide, umeclidinium bromide / vilanterol the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing umeclidinium bromide, umeclidinium bromide / vilanterol 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.