1. NAME OF THE MEDICINAL PRODUCT

ANORO Ellipta 62.5/25 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 25 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

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

4.2 Posology and method of administration

Posology

Adults

The recommended dose is one inhalation of ANORO 62.5/25 micrograms once daily.

ANORO should be administered once daily at the same time of the day each day to maintain bronchodilation. The maximum dose is one inhalation of ANORO 62.5/25 micrograms once daily.

Special populations

Elderly patients
No dosage adjustment is required in patients over 65 years.

Renal impairment
No dosage adjustment is required in patients with renal impairment.

Hepatic impairment
No dosage adjustment is required in patients with mild or moderate hepatic impairment. The use of ANORO has not been studied in patients with severe hepatic impairment and should be used with caution.

Paediatric population

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

Method of administration

ANORO is for inhalation use only.

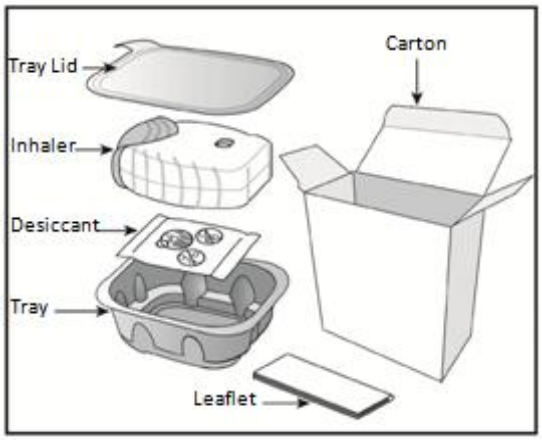
Instructions for use:

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

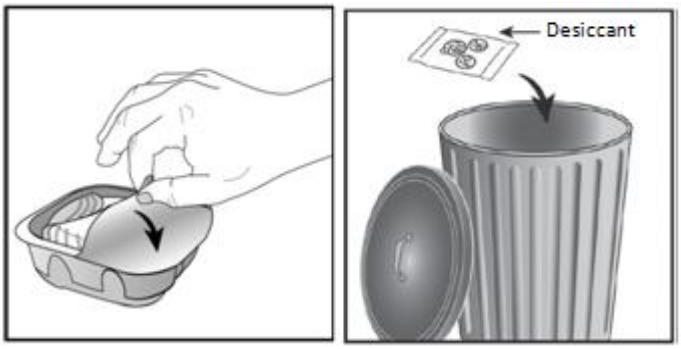
The ELLIPTA inhaler contains pre-dispensed doses and is ready to use.

When the patient first uses the Ellipta inhaler the patient does not need to check that it is working properly, and the patient does not need to prepare it for use in any special way. The patient just has to follow the instructions below.

The Ellipta inhaler carton contains



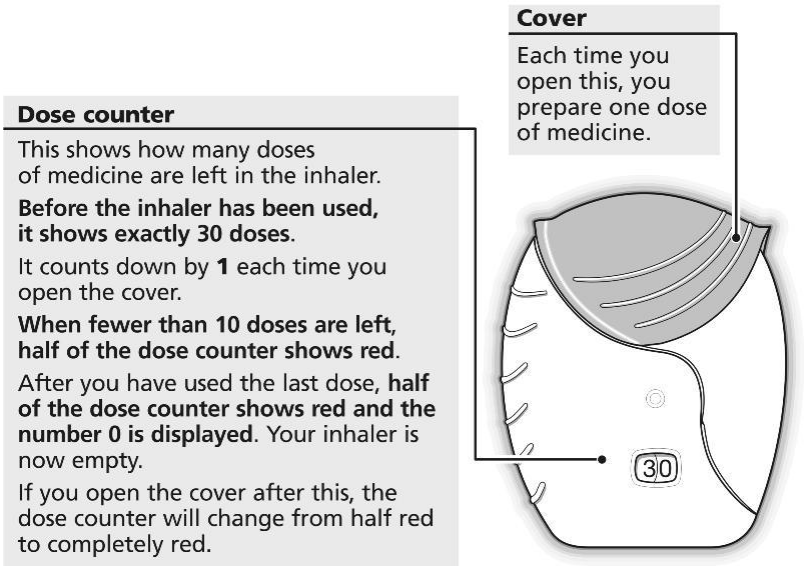
The inhaler is packaged in a tray. The patient should be advised to not open the tray until they are ready to inhale a dose. When the patient is ready to use the inhaler, the lid should be peeled back to open the tray. The tray contains a desiccant sachet, to reduce moisture. The desiccant sachet should be thrown away and it should not be open, eaten or inhaled.



The inhaler will be in the ‘closed’ position when it is first taken out of its sealed tray. The patient should be advised not to open the inhaler until ready to inhale a dose of medicine. 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 used. The tray can be discarded after first opening.

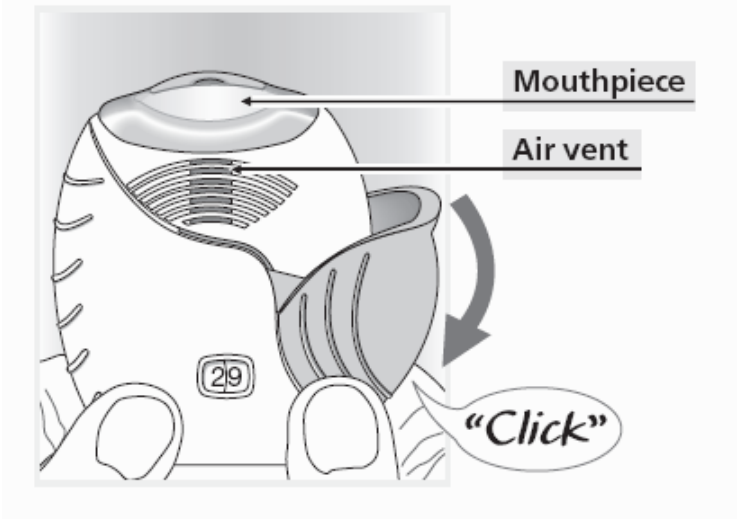
If the inhaler cover is opened and closed without inhaling the medicinal product, the dose will be lost. The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.

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



a) Prepare a dose

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



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

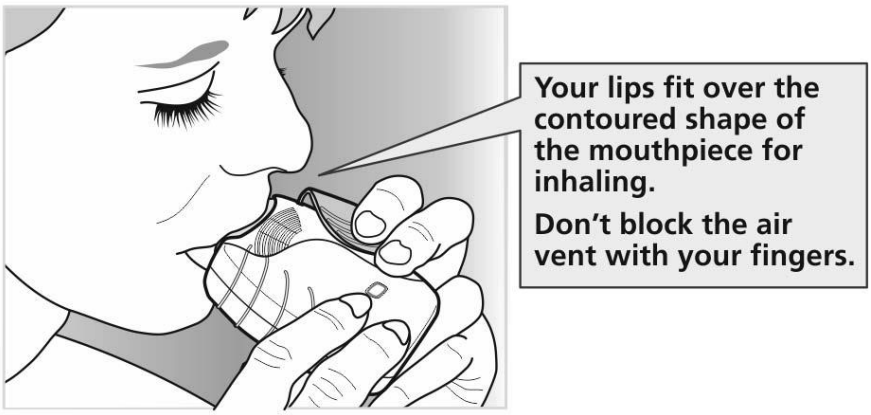
The dose counter counts down by 1 to confirm. If the dose counter does not count down as the "click" is heard, the inhaler will not deliver a dose and should be taken back to a pharmacist for advice.

The inhaler should not be shaken at any time.

b) How to inhale the medicinal product

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

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

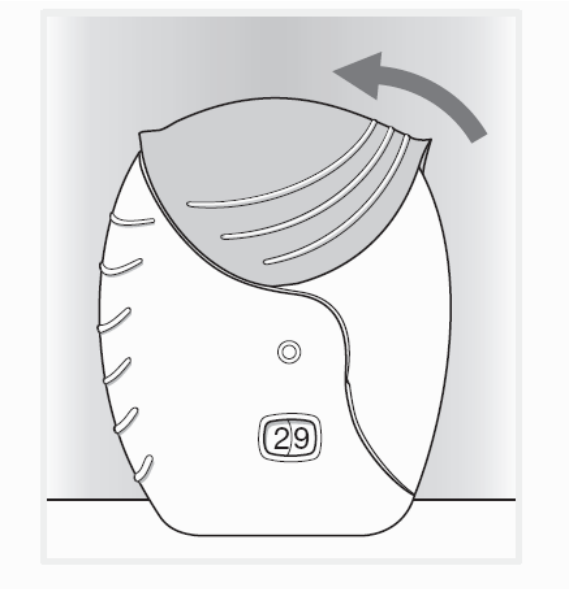


- Inhale with one long, steady, deep breath in. This breath should be held in for as long as possible (at least 3-4 seconds).
- Remove the inhaler from the mouth.
- Breathe out slowly and gently.

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

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

c) Close the inhaler



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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

Paradoxical bronchospasm
As with other inhalation therapies, administration of umeclidinium/vilanterol may produce paradoxical bronchospasm that may be life-threatening. Treatment with umeclidinium/vilanterol should be discontinued immediately if paradoxical bronchospasm occurs 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. 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
Consistent with 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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-adrenergic blockers
Medicinal products containing beta-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 $AUC_{(0-t)}$ 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 drug 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 section 4.4 and section 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 with umeclidinium/vilanterol was nasopharyngitis (9%).

Tabulated summary of adverse reactions
The safety profile of ANORO 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 62.5/25 micrograms in 24-week studies, 832 patients received a higher dose of 125/25 micrograms in 24-week studies and 226 patients received 125/25 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	Common
	Sinusitis	Common
	Nasopharyngitis	Common
	Pharyngitis	Common
	Upper respiratory tract infection	Common
Immune system disorders	Hypersensitivity reactions including:	
	Rash	Uncommon
	Anaphylaxis, angioedema and urticaria	Rare
Nervous system disorders	Headache	Common
	Tremor	Uncommon
	Dysgeusia	Uncommon
Eye disorders	Vision blurred	Rare
	Glaucoma	Rare
	Intraocular pressure increased	Rare
Cardiac disorders	Atrial fibrillation	Uncommon
	Supraventricular tachycardia	Uncommon
	Rhythm idioventricular	Uncommon
	Tachycardia	Uncommon
	Supraventricular extrasystoles	Uncommon
	Palpitations	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Oropharyngeal pain	Common
	Paradoxical bronchospasm	Rare
	Dysphonia	Rare
Gastrointestinal disorders	Constipation	Common
	Dry mouth	Common
Skin and subcutaneous tissue disorders	Rash	Uncommon
Renal and urinary disorders	Urinary retention	Rare
	Dysuria	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.

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, 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 ($beta_2$-adrenergic agonist).
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 ANORO over time.

[*] 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.

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 125/25 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 125/25 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 125/25 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 125/25 micrograms and 500/100 micrograms respectively.

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 62.5/25 micrograms once daily in one 6-month study, or in a further 55 patients who received umeclidinium/vilanterol 125/25 micrograms once daily in another 6-month study and 226 patients who received 125/25 micrograms once daily in the 12-month study.

Clinical efficacy

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
ANORO 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, ANORO demonstrated statistically significant improvements in trough FEV_1 (primary endpoint) at Week 24 compared with placebo and each monotherapy component treatment arm. In addition, ANORO 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:
ANORO 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 ANORO (58%) compared with placebo (41%) and each monotherapy component (53% for umeclidinium and 51% for vilanterol).

Health-related quality of life:
ANORO 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). ANORO 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 ANORO (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 ANORO 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 ANORO and tiotropium; 49% and 54% for ANORO 62.5/25 micrograms and 52% and 55% for tiotropium.

Use of rescue medication
ANORO 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, ANORO reduced the use of rescue medication with salbutamol compared with tiotropium, with statistically significant reductions observed in two of the studies (see Table 1). ANORO 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 ANORO 62.5/25 mcg	Treatment difference[1] (95% confidence intervals, p-value)			
	Trough FEV_1 (ml)	**TDI Focal Score**	**SGRQ Total Score**	**Use of rescue medication[3]**
ANORO (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*
ANORO (N = 413) versus Umeclidinium 62.5 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*
ANORO (N = 413) versus Vilanterol 25 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
ANORO (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
ANORO (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
ANORO (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 higher dose of umeclidinium/vilanterol (125/25 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 ANORO dose and provided additional supportive evidence for the efficacy of ANORO.

COPD exacerbations
ANORO reduced the risk of a COPD exacerbation by 50% compared with placebo (based analysis of time to first exacerbation: Hazard Ratio (HR) 0.5, p=0.004*); by 20% compared with umeclidinium (HR 0.8, p=0.391); and by 30% compared with vilanterol (HR 0.7, p=0.121). From the three active-comparator studies, the risk of a COPD exacerbation compared with tiotropium was reduced by 50% in one study (HR 0.5, p=0.044) and was increased by 20% and 90% in two studies (HR 1.2, p=0.709 and HR 1.9, 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.

* 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.

Exercise endurance and lung volumes
ANORO 62.5/25 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, ANORO 62.5/25 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 ANORO 62.5/25 micrograms and placebo was 21.9 seconds (p=0.234) at Week 12.

ANORO 62.5/25 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, ANORO 62.5/25 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[*]).

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. *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

[*] 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.

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.

Characteristics in specific groups of healthy volunteers or patients

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 nonclinical 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 62.5 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 25 micrograms based on AUC, respectively.

Reproductive toxicity

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 62.5 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 25 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 is indicated on the packaging.

In-use shelf-life: 6 weeks

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.

6.4 Special precautions for storage

Do not store above 30°C.

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

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

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

6.5 Nature and contents of container

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

The inhaler contains two aluminium foil laminate blisters of 7 and 30 doses.

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

Pack sizes of 7 and 30 dose inhalers.

6.6 Special precautions for disposal and other handling

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

For instructions for handling, see section 4.2.

7. PRODUCT REGISTRATION HOLDER

GlaxoSmithKline Pharmaceutical Sdn Bhd
Level 6, Quill 9
No 112, Jalan Semangat
Petaling Jaya
Selangor Darul Ehsan
Malaysia

8. MANUFACTURER

GlaxoSmithKline LLC
1011 North Arendell Avenue
Zebulon
North Carolina 27597
USA

9. VERSION NUMBER

Version number: Anoro Ellipta v04
Reference: EUSPC 1 Oct 2015 and GDS06/IPI07
Date of issue: 07 Feb 2017

10. DATE OF REVISION OF THE TEXT

13 February 2017
Anoro Ellipta are trade marks of the GSK group of companies.
Anoro Ellipta was developed in collaboration with Innoviva, Inc.

(Innoviva logo)
(GSK logo)