
ANORO ELLIPTA

Umeclidinium/vilanterol

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed.

A light grey inhaler with a red mouthpiece cover and an integral dose counter. The Ellipta inhaler contains two blister strips, each of which contains a white powder.

CLINICAL PARTICULARS

Indications

ANORO ELLIPTA is indicated for maintenance bronchodilator treatment to relieve symptoms associated with chronic obstructive pulmonary disease (COPD).

Dosage and Administration

ANORO ELLIPTA is for oral inhalation only.

ANORO ELLIPTA should be administered once daily at the same time each day.

Adults

The recommended and maximum dose is one inhalation of *ANORO ELLIPTA* 62.5/25 micrograms once daily.

Children

Use in patients less than 18 years of age is not relevant given the indication for this product.

Elderly

No dosage adjustment is required in patients over 65 years (see *Pharmacokinetics – Special Patient Populations*).

Renal impairment

No dosage adjustment is required in patients with renal impairment (see *Pharmacokinetics – Special Patient Populations*).

Hepatic impairment

No dosage adjustment is required in patients with mild or moderate hepatic impairment. *ANORO ELLIPTA* has not been studied in patients with severe hepatic impairment (see *Pharmacokinetics – Special Patient Populations*).

Contraindications

ANORO ELLIPTA is contraindicated in patients with severe milk-protein allergy, or who have demonstrated hypersensitivity to either umeclidinium, vilanterol or any of the excipients in this product.

Warnings and Precautions

Asthma

ANORO ELLIPTA 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 *ANORO ELLIPTA* may produce paradoxical bronchospasm that may be life-threatening. Treatment with *ANORO ELLIPTA* should be discontinued if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.

Not for acute use

ANORO ELLIPTA 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 and patients. In the event of deterioration of COPD during treatment with *ANORO ELLIPTA*, 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, maybe seen after the administration of sympathomimetic agents and muscarinic receptor antagonists, including *ANORO ELLIPTA*. Therefore, *ANORO ELLIPTA* should be used with caution in patients with severe cardiovascular disease.

Antimuscarinic activity

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

Hypokalaemia

Beta₂-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 *Interactions*).

Hyperglycaemia

Beta₂-adrenergic agonists may produce transient hyperglycaemia 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.

Co-existing conditions

Umeclidinium/vilanterol should be used with caution in patients with convulsive disorder or thyrotoxicosis, and in patients who are unusually responsive to beta₂-adrenergic agonists.

Interactions

Beta-adrenergic blockers

Medicinal products containing beta-adrenergic blockers may weaken or antagonise the effect of beta₂-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 (40 mg) in healthy volunteers increased mean vilanterol AUC₍₀₋₄₎ 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 4-fold higher dose. An approximately 1.3-fold increase in umeclidinium AUC was observed at 8-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 beta₂-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 beta₂-adrenergic agonist adverse reactions (see sections *Warnings and Precautions* and *Overdose*).

Hypokalaemia

Concomitant hypokalaemia treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta₂-adrenergic agonists, therefore use with caution (see section *Warnings and Precautions*).

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.

Pregnancy and Lactation

Fertility

There are no data on the effects of *ANORO ELLIPTA* on human fertility. Animal studies indicate no effects of umeclidinium or vilanterol on fertility (see *Pre-clinical Safety Data*).

Pregnancy

There are no or limited amount of data from the use of *ANORO ELLIPTA* in pregnant women. Studies in animals have shown reproductive toxicity after inhaled administration of vilanterol (see *Pre-clinical Safety Data*). *ANORO ELLIPTA* should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

Lactation

It is unknown whether umeclidinium or vilanterol are excreted in human milk. However, other beta₂-agonists are detected in human milk. A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breastfeeding or to discontinue *ANORO ELLIPTA* therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *ANORO ELLIPTA* on the ability to perform tasks that require judgement, motor or cognitive skills.

Adverse Reactions

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 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. This includes 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 frequency 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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1,000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1,000$) very rare ($< 1/10,000$) and unknown (cannot be estimated from available data).

<u>MedDRA</u> System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Urinary tract infection	Common
	Sinusitis	Common
	Nasopharyngitis	Common
	Pharyngitis	Common
	Upper respiratory tract infection	Common
Nervous system disorders	Headache	Common
Cardiac Disorders	Atrial Fibrillation	Uncommon
	Supraventricular tachycardia	Uncommon
	Rhythm idioventricular	Uncommon
	Tachycardia	Uncommon
	Supraventricular extrasystoles	Uncommon
Respiratory, Thoracic and Mediastinal	Cough	Common

<u>MedDRA</u> System organ class	Adverse reaction(s)	Frequency
Disorders	Oropharyngeal pain	Common
Gastrointestinal Disorders	Constipation Dry mouth	Common Common

Post-marketing data

<u>MedDRA</u> System organ class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions including: Rash Anaphylaxis, angioedema, and urticaria	Uncommon Rare
Psychiatric disorders	Anxiety	Uncommon
Nervous system disorders	Tremor Dysgeusia	Uncommon Uncommon
Eye disorders	Vision blurred Glaucoma Intraocular pressure increased	Rare Rare Rare
Cardiac disorders	Palpitations	Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Paradoxical bronchospasm Dysphonia	Rare Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Uncommon
Renal and urinary disorders	Urinary retention Dysuria	Rare Rare

Overdose

Symptoms and signs

An overdose of *ANORO ELLIPTA* will likely produce signs and symptoms due to the individual components' actions, consistent with the known inhaled muscarinic antagonist adverse effects (e.g. dry mouth, visual accommodation disturbances and tachycardia) and those seen with overdose of other beta₂-agonists (e.g. tremor, headache and tachycardia).

Treatment

There is no specific treatment for an overdose of *ANORO ELLIPTA*. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of action

Umeclidinium/vilanterol is a combination inhaled long-acting muscarinic receptor antagonist/long-acting beta₂-adrenergic agonist (LAMA/LABA). Following 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 that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic acetylcholine receptors on airway smooth muscle. It demonstrates slow reversibility at the human M₃ muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Vilanterol

Vilanterol is a selective long-acting, beta₂-adrenergic receptor agonist (beta₂-agonist).

The pharmacologic effects of beta₂-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 one placebo controlled clinical efficacy study *ANORO ELLIPTA* increased FEV₁ after the first dose on Day 1 with an improvement compared with placebo of 0.11 L (p<0.001) at 15 minutes following administration. The change from baseline to peak FEV₁ during 0-6 hours post-dose at Day 1 and Week 24 was 0.27 L and 0.32 L respectively for *ANORO ELLIPTA*, compared with 0.11 L (Day 1) and 0.10 L (Week 24) for placebo.

Cardiovascular effects

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 (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, QTcF) 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.

Pharmacokinetics

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 (see *Metabolism; Drug-drug interactions*). 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 2-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 subjects, 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%.

Metabolism

Umeclidinium

In vitro studies showed that umeclidinium is metabolised principally via cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (Pgp) 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 metabolised principally via cytochrome P450 3A4 (CYP3A4) and is a substrate for the Pgp transporter. The primary metabolic routes are O-dealkylation to a range of metabolites with significantly reduced β_1 - and

beta₂-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.

Drug-drug interactions

Available pharmacokinetic data in healthy volunteers and patients with COPD show that the systemic exposure (C_{max} and AUC) and population pharmacokinetic predicted exposures to umeclidinium and vilanterol is unaffected by administration with the umeclidinium/vilanterol combination compared to the components administered separately. Co-administration with the strong CYP3A4 inhibitor ketoconazole (400 mg) 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-agonist related systemic effects on heart rate, blood potassium or QT interval (corrected using the Fridericia method).

Both umeclidinium and vilanterol are substrates of P-glycoprotein (P-gp). The effect of the moderate P-gp transporter inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium 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.

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 subjects, total radioactivity was excreted primarily in faeces (92% of the administered radiolabelled dose or 99% of the recovered radioactivity) by 168 hours post-dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% drug 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 patient 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

Subjects with severe renal impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC), and no evidence of altered protein binding between subjects with severe renal impairment and healthy volunteers.

Hepatic impairment

Subjects with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium/vilanterol has not been evaluated in subjects with severe hepatic impairment.

Other patient characteristics

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.

Clinical Studies

The clinical efficacy of umeclidinium/vilanterol of *ANORO ELLIPTA* administered once daily were 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 ELLIPTA demonstrated improvements in lung function (as defined by change from baseline in trough FEV₁) in several studies. In one 6-month Phase III study, *ANORO ELLIPTA* demonstrated statistically significant improvements in trough FEV₁ (primary endpoint) at Week 24 compared with placebo and each monotherapy component treatment arm. In addition, *ANORO ELLIPTA* demonstrated clinically meaningful and statistically significant improvements in trough FEV₁ 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 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 *ANORO ELLIPTA* (58%) compared with placebo (41%) and each monotherapy component (53% for umeclidinium and 51% for vilanterol).

Health-related quality of life:

ANORO 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). *ANORO 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 *ANORO 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 *ANORO 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 *ANORO* and tiotropium; 49% and 54% for *ANORO* 62.5/25 micrograms and 52% and 55% for tiotropium.

Use of rescue medication:

ANORO ELLIPTA reduced the use of rescue medication with salbutamol compared with placebo and umeclidinium (see Table 1) and demonstrated a higher percentage of days when no rescue medication was needed (on average 36.1%) compared with placebo (on average 21.7%).

In the three 6-month active-comparator-controlled studies, *ANORO 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). *ANORO ELLIPTA*

also demonstrated a higher percentage 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 <i>ANORO ELLIPTA</i> 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 ¹
<i>ANORO</i> (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 (0.13, -0.3) 0.001*
<i>ANORO</i> (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*
<i>ANORO</i> (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
<i>ANORO</i> (N=454) versus tiotropium 18 mcg (N=451) (Study ZEP 117115)	112 (81, 144) <0.001	n/e	-2.10 (-3.61, -0.59) 0.006	-0.5 (-0.7, -0.2) <0.001
<i>ANORO</i> (N=207) versus tiotropium 18 mcg (N=203)	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

(Study DB2113360)				
<i>ANORO</i> (N=217)	60		-0.17	-0.6
versus	(10, 109)		(-2.85, 2.52)	(-1.2, 0.0)
tiotropium 18 mcg (N=215)	0.018*		0.904	0.069
(Study DB2113374)				

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 (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 ELLIPTA* dose and provided additional supportive evidence for the efficacy of *ANORO ELLIPTA*.

COPD exacerbations:

In a 24-week placebo-controlled study in patients with symptomatic COPD, *ANORO 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

ANORO ELLIPTA 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 ELLIPTA* 62.5/25 micrograms demonstrated a statistically significant and clinically relevant improvement (based on a minimally clinically important difference (MCID) between 45 to 85 seconds) over placebo in exercise endurance time (EET) obtained 3 hours after dosing at Week 12 (69.5 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 ELLIPTA* 62.5/25 micrograms and placebo was 21.9 seconds ($p=0.234$) at Week 12.

ANORO ELLIPTA 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: -466ml and -643ml respectively and functional residual capacity: -351ml and -522ml respectively; all $p < 0.001$). In the second study, *ANORO ELLIPTA* 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: 198ml and 238ml respectively, residual volume: -295ml and -351ml respectively and functional residual capacity: -238ml and -302ml respectively); all $p < 0.001^*$).

Pre-clinical Safety Data

In non-clinical studies with umeclidinium and vilanterol, findings were those typically associated with the primary pharmacology of either muscarinic receptor antagonists or beta₂-agonists respectively and/or local irritancy. Administration of umeclidinium and vilanterol in combination did not result in any new toxicity. The following statements reflect studies conducted on the individual components.

Carcinogenesis/mutagenesis

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.

Genetic toxicity studies indicate vilanterol does not represent a genotoxic hazard to humans. Consistent with findings for other beta₂-agonists, in lifetime inhalation studies vilanterol 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 Toxicology

Neither umeclidinium nor vilanterol had any adverse effects on male or female fertility in rats.

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 62.5 micrograms umeclidinium, based on AUC).

Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, vilanterol caused effects similar to those seen with other beta₂-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 25 micrograms vilanterol based on AUC.

PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose monohydrate (which contains milk protein)
(25 milligrams lactose monohydrate per dose)

Magnesium stearate

Incompatibilities

No incompatibilities have been identified.

Shelf Life

The expiry date is indicated on the packaging.

In-use shelf-life:

Following removal from the tray, the product may be stored for a maximum period of 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.

Special Precautions for Storage

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

Nature and Contents of Container

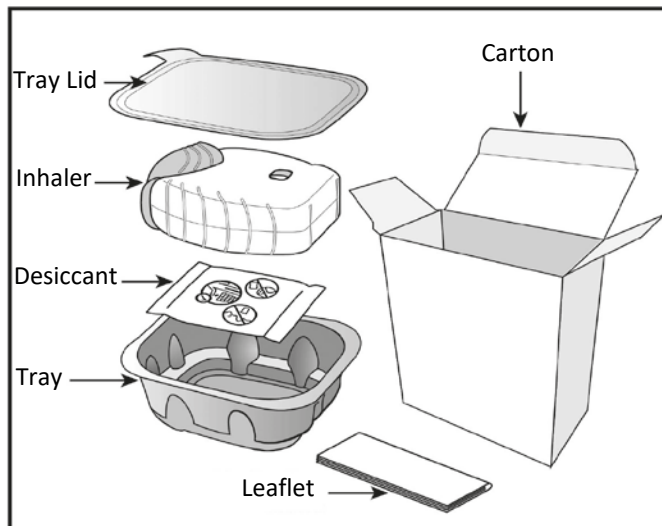
The plastic Ellipta inhaler consists of a light grey body, a red mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

The inhaler contains two strips of either 7 or 30 regularly distributed blisters, with one strip containing 62.5 micrograms of umeclidinium and the other strip containing 25 micrograms of vilanterol.

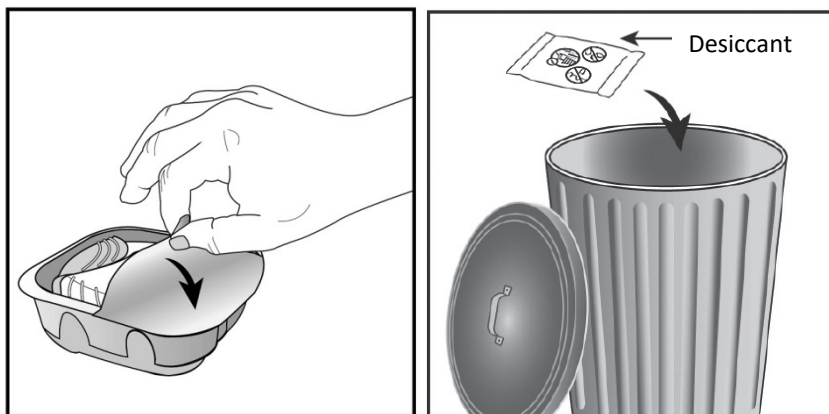
Instructions for Use

When you first use the Ellipta inhaler you do not need to check that it is working properly, and you do not need to prepare it for use in any special way. Just follow the instructions below.

Your Ellipta inhaler carton contains



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



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

The step-by-step instructions shown below for the 30-dose (30 day supply) Ellipta inhaler also apply to the 7-dose (7 day supply) Ellipta inhaler.

a) Read this before you start

If you open and close the cover without inhaling the medicine, you will lose the dose.

The lost dose will be securely held inside the inhaler, but it will no longer be available.

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

Dose counter

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

Before the inhaler has been used, it shows exactly 30 doses.

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

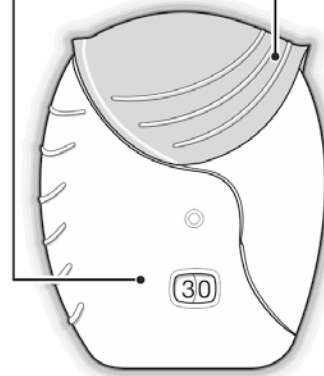
When fewer than 10 doses are left, half of the dose counter shows red.

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

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

Cover

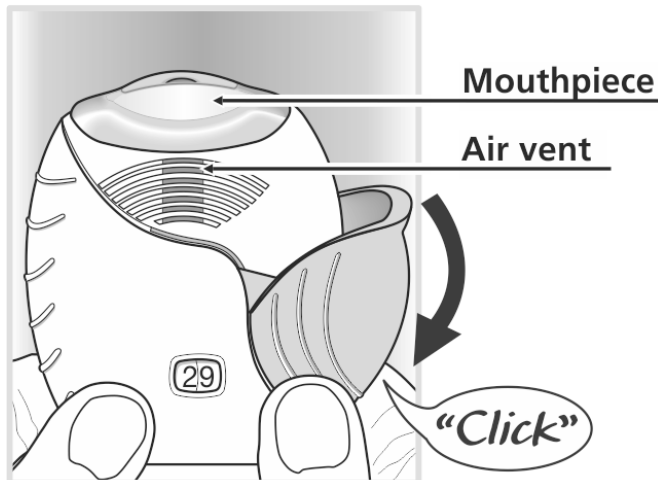
Each time you open this, you prepare one dose of medicine.



b) Prepare a dose

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

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



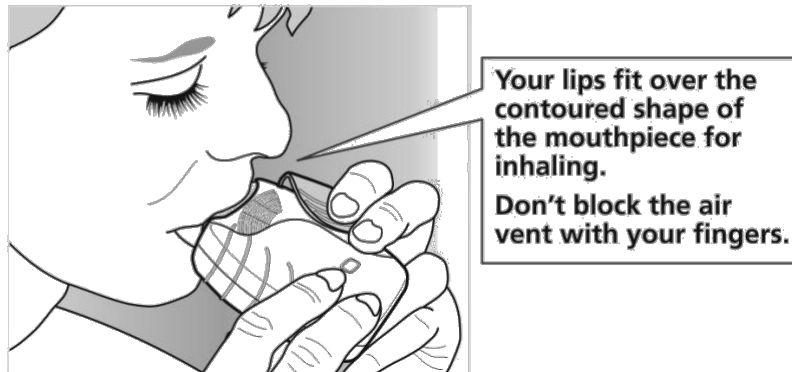
Your medicine is now ready to be inhaled.

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.**
- **Do not shake the inhaler at any time.**

c) Inhale your medication

- **While holding the inhaler away from your mouth, breathe out as far as is comfortable.**
Don't breathe out into the inhaler.
- **Put the mouthpiece between your lips, and close your lips firmly around it.**
Don't block the air vent with your fingers.

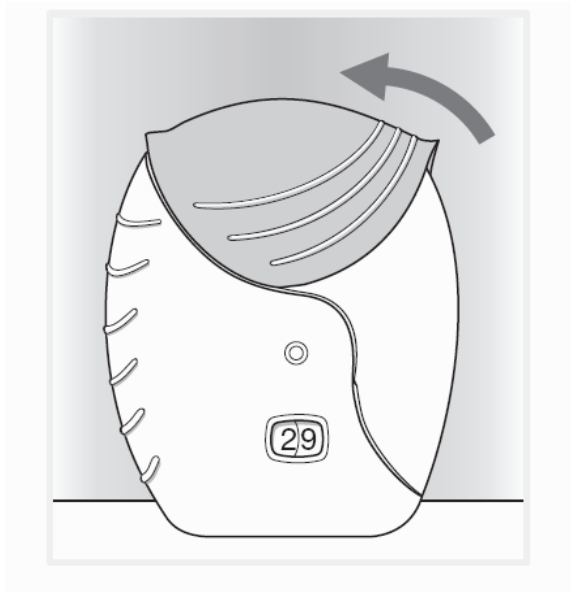


- **Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).**
- **Remove the inhaler from your mouth.**
- **Breathe out slowly and gently.**

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.

d) Close the inhaler



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

Not all presentations are available in every country.

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ANORO ELLIPTA was developed in collaboration with Theravance, Inc.

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