Umeclidinium bromide + Vilanterol (as trifenatate)

Anoro® Ellipta®

62.5 mcg / 25 mcg New Dry Powder Inhaler

Bronchodilator (Long-acting muscarinic receptor antagonist / Long -acting beta$_2$ -adrenergic agonist combination)

PRODUCT DESCRIPTION

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* New Dry Powder Inhaler: 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 trifenatate). 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 trifenatate).

Inhalation powder, pre-dispensed.
The plastic device *Ellipta®* inhaler consists of a light grey inhaler with a red mouthpiece cover and an integral dose counter. The inhaler contains two blister strips, each of which contains a white powder.

PHARMACOLOGIC PROPERTIES

Pharmacodynamics

Mechanism of action

Umeclidinium bromide + Vilanterol (as trifenatate) is a combination inhaled long-acting muscarinic receptor antagonist/long-acting beta$_2$-adrenergic agonist (LABA/LAMA). 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 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, beta$_2$-adrenergic receptor agonist (beta$_2$-agonist).
The pharmacologic effects of beta$_2$-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 two placebo controlled clinical efficacy studies Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* increased FEV_1 after the first dose on Day 1 with an improvement of 0.11 L and 0.13 L at 15 minutes following dosing with 62.5/25 micrograms and 113/22 micrograms respectively, compared with placebo (both $p<0.001$). The change from baseline to peak FEV_1 during 0-6 hours post-dose at Day 1 and Week 24 was 0.27 L and 0.32 L with 62.5/25 micrograms respectively, and 0.31 L and 0.34 L with 113/22 micrograms respectively, compared with 0.11 L and 0.09 L (Day 1) and 0.10 L and 0.06 L (Week 24) for placebo.

Cardiovascular effects

The effect of vilanterol/umeclidinium on the QT interval was evaluated in a placebo and moxifloxacin controlled QT study. Following once daily administration of pre-dispensed doses of vilanterol/umeclidinium 125/25 micrograms or 500/100 micrograms for 10 days in 103 healthy volunteers, no clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) was observed.
In addition, no clinically significant effects of vilanterol/umeclidinium on cardiac rhythm were observed on 24-hour Holter monitoring in 108 patients with COPD treated for up to 6 months (of whom 53 patients received 62.5/25 micrograms and 55 patients received 113/22 micrograms once daily), and in a further 226 patients who received 113/22 micrograms once daily for up to 12 months.

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. Umeclidinium systemic exposure following inhaled administration of 113 micrograms was approximately twice the systemic exposure following 62.5 micrograms.

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 $beta_1$- and $beta_2$- 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 vilanterol/umeclidinium 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. vilanterol/umeclidinium 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 safety and efficacy of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* administered once daily were evaluated in seven Phase III clinical studies in adult patients with a clinical diagnosis of COPD; four were 6-month

primary efficacy studies (DB2113361, DB2113373, DB2113360 and DB2113374), two were 12-week exercise endurance studies (DB2114417 and DB2114418) and one study (DB2113359) evaluated the safety of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* administered over a 12-month treatment period.

Placebo Controlled Studies

In the two 6-month studies, DB2113361 and DB2113373, both Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* doses demonstrated statistically significant improvements in lung function (as defined by change from baseline trough FEV_1 at Week 24) compared with placebo (see *Table 1*). In both studies, bronchodilatory effects with Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* compared with placebo were evident after the first day of treatment and were maintained over the 24 week treatment period.

Table 1. Primary efficacy endpoint at Week 24 (Studies DB2113361 and DB2113373)

	Trough FEV_1 (L)		
			Difference from Placebo
	Baseline (SD)	**Change from baseline (SE)**	**Treatment Difference (95% CI) p-value**
Study DB2113373			
Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 62.5/25 mcg OD (n= 413)	1.28 (0.56)	0.17 (0.01)	0.17 (0.13,0.21) <0.001
Placebo (n=280)	1.20 (0.47)	0.00 (0.02)	-
Study DB2113361			
Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 mcg OD (n= 403)	1.26 (0.48)	0.21 (0.01)	0.24 (0.20, 0.28) <0.001
Placebo (n= 275)	1.26 (0.47)	-0.03 (0.02)	-

Abbreviations: CI= confidence interval; FEV_1= forced expiratory volume in 1 second; L= litres; mcg= micrograms; n= number randomized to treatment; OD= once daily; SD= standard deviation; SE= standard error.

Each Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* dose (62.5/25 micrograms and 113/22 micrograms) demonstrated a statistically significant greater improvement from baseline in weighted mean FEV_1 over 0-6 hours post-dose at Week 24 compared with placebo (0.24 L and 0.29 L respectively; both p<0.001).

Statistically significant improvements from placebo in the Transitional Dyspnoea Index (TDI) focal score at Week 24 were demonstrated for both Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* doses (1.2 units for 62.5/25 micrograms and 1.0 units for 113/22 micrograms; both p<0.001). The percentage of patients receiving Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* that responded with a minimum clinically important difference (MCID) of ≥1 unit TDI focal score at Week 24 was 58% (226/389) for 62.5/25 micrograms and 49% (183/371) for 113/22 micrograms compared with 41% (106/260) and 30% (70/234) for placebo.

Statistically significant improvements from placebo in the change from baseline in total score at Week 24 for the St. George's Respiratory Questionnaire (SGRQ), a disease-specific health status measure, were also demonstrated for both Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* doses (-5.51 units for 62.5/25 micrograms and -3.60 units for 113/22 micrograms; both p≤0.001). The percentage of patients receiving vilanterol/umeclidinium that responded with a reduction of ≥4 units (MCID) in SGRQ total score was 49% (188/381) for 62.5/25 micrograms and 49% (173/356) for 113/22 micrograms compared with 34% (86/254) and 37% (80/219) for placebo.

In addition, patients treated with Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* required less rescue salbutamol than those treated with placebo (on average a reduction of 0.8 puffs per day for the 62.5/25 micrograms dose and a reduction of 1.5 puffs per day for the 113/22 micrograms dose) and differences from placebo for both doses were statistically significant (both p≤0.001). Throughout the 24-week studies, patients treated with Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* had more days when no rescue medication was needed (on average 36.1% for the 62.5/25 micrograms dose and 44.9% for the 113/22 micrograms dose) compared with placebo (on average 21.7% and 28.3%; no formal statistical analysis was performed on this endpoint).

In the 12-month study the improvement in change from baseline in trough FEV_1 at Month 12 in patients receiving Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 micrograms compared with placebo was 0.23 L (95% CI=0.15 to 0.31 L) demonstrating that bronchodilatory efficacy was maintained when administered over a one year period. Treatment with Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 micrograms resulted in a lower risk of COPD exacerbation compared with placebo (analysis of time to first exacerbation; Hazard Ratio 0.4, 95% CI=0.3 to 0.8, risk reduction 60%).

Tiotropium Comparator Studies

In study DB2113360 treatment with either dose of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)*, 113/22 micrograms or 62.5/25 micrograms, provided statistically significant improvements in trough FEV_1 compared with tiotropium at Week 24 (see *Table 2*). Study DB2113374 demonstrated that treatment with umeclidinium/ vilanterol 113/22 micrograms provided statistically significant improvements in trough FEV_1 at Week 24 compared with tiotropium (see *Table 2*).

Each Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* dose (62.5/25 micrograms and 113/22 micrograms) in Study DB2113360 showed a statistically significant greater improvement (of 0.07 L and 0.08 L,

respectively) in change from baseline in weighted mean FEV_1 over 0-6 hours at Week 24 compared with tiotropium (both p≤0.005). Each Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* dose (62.5/25 micrograms and 113/22 micrograms) in Study DB2113374 showed a clinically meaningful improvement of 0.10 L in change from baseline in weighted mean FEV_1 over 0-6 hours at Week 24 compared with tiotropium.
All treatments (including tiotropium) improved measures of dyspnoea (TDI focal score) and health-related quality of life (SGRQ) compared with baseline. Statistically significant improvements in rescue salbutamol use over weeks 1-24 were observed for each Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* dose over tiotropium in study DB2113360 (-0.7 puffs per day for 62.5/25 micrograms and -0.6 puffs per day for 113/22 micrograms; both p≤0.031), and improvements were observed for Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 micrograms over tiotropium in study DB2113374 (-1.1 puffs per day).

Table 2. Primary efficacy endpoint at Week 24 (Studies DB2113360 and DB2113374)

	Trough FEV_1 (L)		
			Difference from tiotropium
	Baseline (SD)	Change from baseline (SE)	Treatment Difference (95% CI) p-value
Study DB2113360			
Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 mcg OD (n=208)	1.30 (0.48)	0.21 (0.02)	0.09 (0.04,0.14) <0.001
Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)*62.5/25 mcg OD (n=207)	1.32 (0.53)	0.21 (0.02)	0.09 (0.04,0.14) <0.001
Tiotropium 18 mcg OD (n=203)	1.29 (0.53)	0.12 (0.02)	-
Study DB2113374			
Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 mcg OD (n=215)	1.14 (0.47)	0.22 (0.02)	0.07 (0.03, 0.12) 0.003
Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 62.5/25 mcg OD (n=216)	1.16 (0.48)	0.21 (0.02)	0.06 (0.01, 0.11) 0.018*
Tiotropium 18 mcg OD (n=215)	1.16 (0.45)	0.15 (0.02)	

Abbreviations: CI= confidence interval; FEV_1= forced expiratory volume in 1 second; L= litres; mcg= micrograms; n= number randomized to treatment; OD= once daily; SD= standard deviation; SE= standard error;
*As a result of a prior test in the predefined testing hierarchy not achieving statistical significance, statistical significance cannot be inferred for this comparison.

Additional efficacy

Pooled data from the four 6-month primary efficacy studies demonstrated that, in patients demonstrating responsiveness to salbutamol at study entry, greater improvements from placebo in trough FEV_1 and greater reductions from placebo in rescue salbutamol use were achieved for umeclidinium/ vilanterol 113/22 micrograms (0.28 L at Week 24 and 1.82 puffs per day over Weeks 1 to 24, respectively) than were achieved for Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 62.5/25 micrograms (0.23 L at Week 24 and 1.18 puffs per day over Weeks 1 to 24, respectively). No formal statistical comparisons between the two Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* doses were performed.

Supportive 3-month exercise endurance studies

Exercise endurance was evaluated with the endurance shuttle walk test (ESWT) in adult COPD patients with hyperinflation (functional residual capacity [FRC] >120%) in two replicate, 12-week clinical studies.
In one study (DB2114418), treatment with Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 62.5/25 micrograms and 113/22 micrograms demonstrated statistically significant improvements over placebo in exercise endurance time (EET) obtained 3 hours after dosing at Week 12 of 69.4 seconds (p=0.003) and 65.8 seconds (p=0.005) respectively. Improvement in EET with each dose compared with placebo was seen at Day 2 and was sustained at Week 6 and Week 12. In the second study (DB2114417), treatment with Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 62.5/25 micrograms and 113/22 micrograms did not show statistically significant improvements in EET (21.9 seconds and 32.4 seconds respectively; p>0.05).
In Study DB2114418, each Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* dose showed statistically significant improvements compared to placebo in change from baseline in trough FEV_1 at Week 12 (of 0.24 L for 62.5/25 micrograms and 0.26 L for 113/22 micrograms, both p<0.001), and statistically significant improvements compared to placebo in change from baseline in lung volume measures at 3 hours post dose and at trough at Week 12 (inspiratory capacity: 0.23 to 0.33 L, residual volume: -0.37 to -0.64 L and functional residual capacity: -0.25 to -0.52 L; all p<0.001). In Study DB2114417, each Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* dose showed clinically meaningful improvements compared to placebo in change from baseline in trough FEV_1 at Week 12 (of 0.21 L

for 62.5/25 micrograms and 0.17 L for 113/22 micrograms), and improvements compared to placebo in change from baseline in lung volume measures at 3 hours post dose and at trough at Week 12 (inspiratory capacity: 0.17 to 0.24 L, residual volume: -0.29 to -0.54 L and functional residual capacity: -0.24 to -0.47 L).

Pre-clinical Safety Data

In nonclinical studies with umeclidinium and vilanterol, findings were those typically associated with the primary pharmacology of either muscarinic receptor antagonists or beta$_2$-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 ≥ 13 or ≥ 11-fold, times the human clinical exposure of umeclidinium 113 micrograms, based on AUC, respectively.

Genetic toxicity studies indicate vilanterol does not represent a genotoxic hazard to humans. Consistent with findings for other beta$_2$-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 22 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 40-times the human clinical exposure of 113 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 beta$_2$-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 22 micrograms vilanterol based on AUC.

INIDICATIONS

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* is indicated for maintenance bronchodilator treatment to relieve symptoms associated with chronic obstructive pulmonary disease (COPD).

DOSAGE AND ADMINISTRATION

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* is for oral inhalation only.

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* should be administered once daily at the same time of the day each day.

Adults

The recommended dose is one inhalation of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®))* 62.5/25 micrograms once daily.

Use of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 113/22 micrograms once daily in some patients has been shown to provide additional clinical benefit with regard to lung function and rescue medication use (see *Clinical studies; Additional efficacy*). The maximum dose is one inhalation of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)*113/22 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. Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* has not been studied in patients with severe hepatic impairment (see *Pharmacokinetics — Special Patient Populations*).

CONTRAINDICATIONS

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* is contraindicated in patients with severe milk-protein allergy.

WARNINGS AND PRECAUTIONS

The use of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* has not been studied in patients with asthma, and is not recommended in this patient population.

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* is intended for the maintenance treatment of COPD. It should not be used for the relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting bronchodilator. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

As with other inhalation therapies, administration of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* may produce paradoxical bronchospasm that may be life-threatening. Treatment with Umeclidinium bromide + Vilanterol

(as trifenatate) *(Anoro® Ellipta®)* should be discontinued if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.
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 Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)*. Therefore, Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* should be used with caution in patients with severe cardiovascular disease.

Consistent with its antimuscarinic activity, Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* should be used with caution in patients with narrow-angle glaucoma or urinary retention.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* on the ability to perform tasks that require judgement, motor or cognitive skills.

DRUG INTERACTIONS

Interaction with beta-blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta2-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.

Interaction with CYP3A4 inhibitors

Vilanterol, a component of Umeclidinium Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)*, is cleared by CYP3A4 mediated extensive first-pass metabolism in the gastrointestinal tract and in the liver.
Care is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole) as there is potential for an increased systemic exposure to vilanterol, which could lead to an increase in the potential for adverse reactions (see *Pharmacokinetics*).

PREGNANCY AND LACTATION

Fertility

There are no data on the effects of Umeclidinium bromide + Vilanterol (as trifenatate) *(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 Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* in pregnant women. Studies in animals have shown reproductive toxicity after inhaled administration of vilanterol (see *Pre-clinical Safety Data*). Umeclidinium bromide + Vilanterol (as trifenatate) *(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 $beta_2$-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 Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Adverse Reactions

Clinical trial data

The safety profile of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* is based on 2,454 patients with COPD who received at least one dose of Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* during clinical studies. This includes 1,124 patients who received 62.5/25 micrograms and 1,330 patients who received 113/22 micrograms, all once daily. The adverse reactions identified from these studies are presented in the table below. Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000).

MedDRA System organ class	**Adverse reaction(s)**	**Frequency**
Infections and infestations	Pharyngitis	Common
Cardiac Disorders	Atrial Fibrillation Tachycardia	Uncommon Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Cough	Common
Gastrointestinal Disorders	Constipation Dry mouth	Common Common

Post-marketing data

There are no relevant data available.

OVERDOSAGE AND TREATMENT

No data from clinical studies are available regarding overdose with umeclidinium/ vilanterol.

Symptoms and signs

An overdose of Umeclidinium bromide + Vilanterol (as trifenatate) *(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 Umeclidinium bromide + Vilanterol (as trifenatate) *(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.

STORAGE CONDITIONS

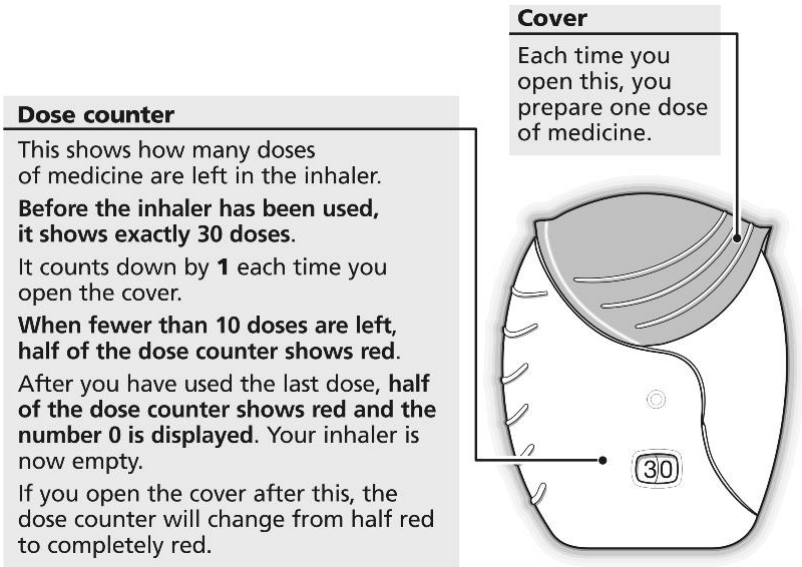
Store at temperatures not exceeding 30^{o}C
Following removal from the tray, the product may be stored for a maximum period of 6 weeks.

INSTRUCTIONS FOR USE/HANDLING

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.
The inhaler is packaged in a tray containing a desiccant packet, to reduce moisture. Throw this packet away — don't eat or inhale it.
When you take the inhaler out of the sealed tray, it will be in the 'closed' position. Don't open it until you are ready to inhale a dose of medicine.
The step-by-step instructions shown below for the 30-dose Ellipta inhaler also apply to the 7-dose Ellipta inhaler.

a) Read this before you start

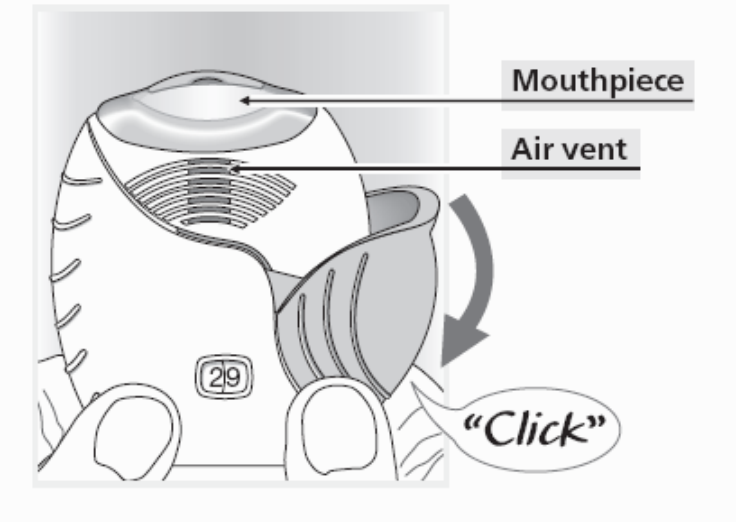
If you open and close the cover without inhaling the medicine, you will lose the dose.
The lost dose will be securely held inside the inhaler, but it will no longer be available.
It is not possible to accidentally take extra medicine or a double dose in one inhalation.



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".



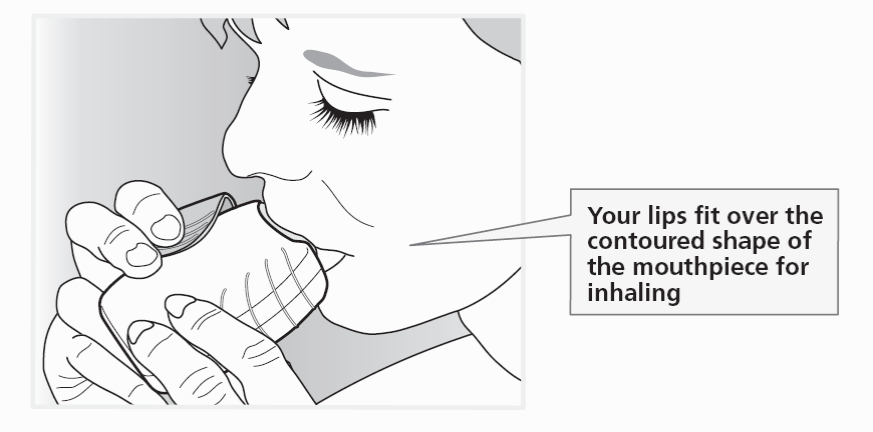
Your medicine is now ready to be inhaled.
The dose counter counts down by 1 to confirm.

- 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.

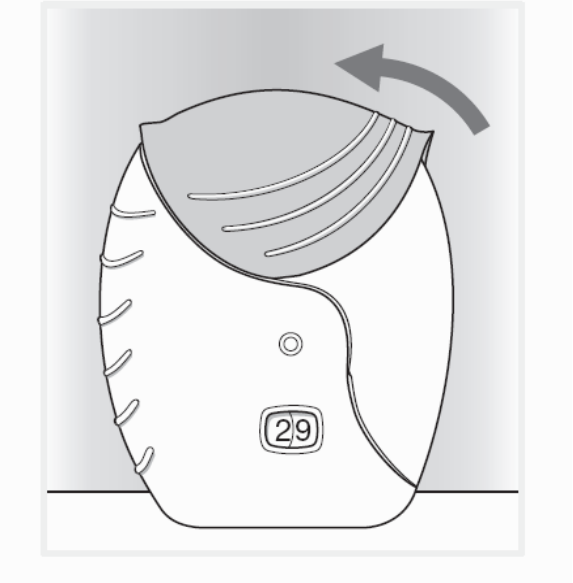


- Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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

d) Close the inhaler

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



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

AVAILABILITY

Umeclidinium bromide + Vilanterol (as trifenatate) *(Anoro® Ellipta®)* 62.5/25 micrograms New Dry Powder Inhaler: Blister pack fitted in a plastic device *Ellipta®* inhaler enclosed in sealed foil laminate tray 30 doses

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 packet. The tray is sealed with a peelable foil lid.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep out of reach of children.

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