ANORO ELLIPTA

Umeclidinium/vilanterol

1. NAME OF THE MEDICINAL PRODUCT

ANORO ELLIPTA

Umeclidinium/vilanterol

2. 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 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).

3. 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.

4. CLINICAL PARTICULARS

4.1 Indications

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

4.2 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).

4.3 Contraindications

ANORO ELLIPTA is contraindicated in patients with severe milk-protein allergy.

4.4 Warnings and Precautions

The use of *ANORO ELLIPTA* has not been studied in patients with asthma, and is not recommended in this patient population.

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 *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.

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.

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

4.5 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 *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).

4.6 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 foetus.

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.

4.7 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.

4.8 Adverse Reactions

Clinical trial data

The safety profile of *ANORO ELLIPTA* is based on approximately 3,000 patients with COPD who received doses of umeclidinium/vilanterol 62.5/25 micrograms or greater for up to one year during clinical studies. This includes approximately 1,600 patients who received 62.5/25 micrograms and approximately 1,300 patients who received 125/25 micrograms, both once daily.

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	Urinary tract infection Sinusitis Nasopharyngitis Pharyngitis Upper respiratory tract infection	Common Common Common Common Common
Cardiac Disorders	Atrial Fibrillation Supraventricular tachycardia Tachycardia	Uncommon Uncommon Uncommon
Respiratory, Thoracic and Mediastinal Disorders	Cough Oropharyngeal pain	Common Common
Gastrointestinal Disorders	Constipation Dry mouth	Common Common

Post-marketing data

MedDRA **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 Headache	Uncommon Uncommon Rare
Eye disorder	Vision blurred Glaucoma Intraocular pressure increased Eye pain	Rare Rare Rare Rare
Cardiac disorders	Palpitations	Uncommon
Respiratory, Thoracic and Mediasinal Disorders	Paradoxical bronchospasm Dysphonia	Rare Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Uncommon

Renal and urinary disorders	Urinary retention Dysuria	Rare Rare

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 FEV_1 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 FEV_1 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 moxifloxacin controlled QT study involving once daily administration of umeclidinium/vilanterol 125/25 micrograms or 500/100 micrograms 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. No clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) was observed.

In addition, no clinically significant effects of umeclidinium/vilanterol on cardiac rhythm were observed on 24-hour Holter monitoring in 281 patients who received umeclidinium/vilanterol 125/25 micrograms once daily for up to 12 months.

5.2 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 beta1- 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 safety and efficacy of *ANORO ELLIPTA* administered once daily were evaluated in eight Phase III clinical studies in adult patients with a clinical diagnosis of COPD; five were 6-month efficacy studies (DB2113361, DB2113373, DB2113360, DB2113374 and ZEP117115), two were 12-week exercise endurance studies (DB2114417 and DB2114418) and one study (DB2113359) evaluated the safety of umeclidinium/vilanterol administered over a 12-month treatment period. Studies included *ANORO ELLIPTA* 62.5/25 micrograms and/or umeclidinium/vilanterol 125/25 micrograms, all once daily. Efficacy results for *ANORO ELLIPTA* 62.5/25 micrograms are presented below.

Placebo controlled studies

In a 6-month study, DB2113373, *ANORO ELLIPTA* 62.5/25 micrograms demonstrated a statistically significant improvement in lung function (as defined by change from baseline trough FEV_1 at Week 24) compared with placebo (see Table 1). Bronchodilatory effects with *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 (Study DB2113373)

	Trough FEV_1 (L)		
			Difference from Placebo
	Baseline (SD)	**Change from baseline (SE)**	**Treatment Difference (95% CI) p-value**
Study DB2113373			
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)	-

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

ANORO ELLIPTA 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; $p<0.001$).

A statistically significant improvement from placebo in the Transitional Dyspnoea Index (TDI) focal score at Week 24 was demonstrated for *ANORO ELLIPTA* (1.2 units; $p<0.001$). The percentage of patients receiving *ANORO ELLIPTA* that responded with a minimum clinically important difference (MCID) of ≥ 1unit TDI focal score at Week 24 was 58% (226/389) compared with 41% (106/260) for placebo.

A statistically significant improvement 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, was also demonstrated for *ANORO ELLIPTA* (-5.51 units; $p\leq0.001$). The percentage of patients receiving *ANORO ELLIPTA* that responded with a reduction from baseline of ≥4 units (MCID) in SGRQ total score was 49% (188/381) compared with 34% (86/254) for placebo.

In addition, patients treated with *ANORO ELLIPTA* required less rescue salbutamol than those treated with placebo (on average a statistically significant reduction of 0.8 puffs per day; $p=0.001$). Throughout the 24-week study, patients treated with *ANORO ELLIPTA* had more days when no rescue medication was needed (on average 36.1%) compared with placebo (on average 21.7%; no formal statistical analysis was performed on this endpoint).

Treatment with *ANORO ELLIPTA* 62.5/25 micrograms resulted in a lower risk of COPD exacerbation compared with placebo (analysis of time to first exacerbation: Hazard Ratio (HR) 0.5, 95% CI=0.3 to 0.8, risk reduction 50%, $p=0.004$).

Tiotropium comparator studies

In studies ZEP117115 and DB2113360 treatment with *ANORO ELLIPTA* 62.5/25 micrograms provided statistically significant and clinically meaningful improvements in change from baseline in trough FEV_1 compared with tiotropium at Week 24 (see Table 2). In Study DB2113374, *ANORO ELLIPTA* 62.5/25 micrograms showed a clinically meaningful

improvement in change from baseline in trough FEV_1 compared with tiotropium at Week 24 (see Table 2).

Table 2. Primary efficacy endpoint at Week 24 (Studies ZEP117115, DB2113360 and DB2113374)

	Trough FEV_1 (L)		
			Difference from tiotropium
	Baseline (SD)	**Change from baseline (SE)**	**Treatment Difference (95% CI) p-value**
Study ZEP117115			
ANORO ELLIPTA 62.5/25 mcg OD (n=454)	1.25 (0.49)	0.21 (0.01)	0.11 (0.08,0.14) <0.001
Tiotropium 18 mcg OD (n=451)	1.25 (0.49)	0.09 (0.01)	-
Study DB2113360			
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			
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 receiving 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.

In Studies ZEP117115 and DB2113360 *ANORO ELLIPTA* showed statistically significant greater improvements of 0.11 L and 0.07 L respectively in change from baseline in weighted mean FEV_1 over 0-6 hours at Week 24 compared with tiotropium (both $p \leq 0.005$). In Study DB2113374 *ANORO ELLIPTA* 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.

In Studies DB2113360 and DB2113374, *ANORO ELLIPTA* and tiotropium both improved measures of dyspnoea (TDI focal score) and health-related quality of life (SGRQ) compared with baseline. In the third active-comparator study (ZEP117115), a statistically significant improvement compared with tiotropium in the change from baseline in SGRQ total score at Week 24 was demonstrated for *ANORO ELLIPTA* (-2.10 units; p=0.006). The percentage of patients receiving *ANORO ELLIPTA* that responded with a reduction from baseline of ≥4 units (MCID) in SGRQ total score from this study was 53% (237/445) compared with 46% (196/430) for tiotropium.

Statistically significant improvements in rescue salbutamol use over weeks 1-24 were observed for *ANORO ELLIPTA* over tiotropium in studies ZEP117115 (-0.5 puffs per day; p<0.001) and DB2113360 (-0.7 puffs per day; p=0.022).

Throughout studies ZEP117115, DB2113360 and DB2113374, patients treated with *ANORO ELLIPTA* had, on average, a greater reduction from baseline in the proportion of days when no rescue medication was needed (21.5%, 18.6% and 17.6% respectively) compared with tiotropium (13.3%, 11.7% and 13.4% respectively; no formal statistical analysis was performed on this endpoint).

In Study ZEP117115, treatment with *ANORO ELLIPTA* 62.5/25 micrograms resulted in a lower risk of COPD exacerbation compared with tiotropium (analysis of time to first exacerbation: Hazard Ratio (HR) 0.5, 95% CI=0.3 to 1.0, risk reduction 50%, p=0.044).

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 *ANORO ELLIPTA* 62.5/25 micrograms demonstrated a statistically significant improvement over placebo in exercise endurance time (EET) obtained 3 hours after dosing at Week 12 of 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 (DB2114417), treatment with *ANORO ELLIPTA* 62.5/25 micrograms did not show a statistically significant improvement over placebo in EET (21.9 seconds; p>0.05).

In Study DB2114418, *ANORO ELLIPTA* showed a statistically significant improvement compared to placebo in change from baseline in trough FEV_1 at Week 12 of 0.24 L (p<0.001), and statistically significant improvements compared to placebo in change from baseline in lung volume measures at trough and at 3 hours post dose at Week 12 (inspiratory capacity: 0.24 L and 0.32 L respectively, residual volume: -0.47 L and -0.64 L respectively and functional residual capacity: -0.35 L and -0.52 L respectively; all p<0.001). In Study DB2114417, *ANORO ELLIPTA* showed a clinically meaningful improvement compared to placebo in change from baseline in trough FEV_1 at Week 12 of 0.21 L, and improvements compared to placebo in change from baseline in lung volume measures at trough and at 3 hours post dose at Week 12 (inspiratory capacity: 0.20 L and 0.24 L respectively, residual volume: -0.29 L and -0.35 L respectively and functional residual capacity: -0.24 L and -0.30 L respectively).

5.3 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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

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

Magnesium stearate

6.2 Incompatibilities

No incompatibilities have been identified.

6.3 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.

6.4 Special Precautions for Storage

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

6.5 Nature and Contents of Container

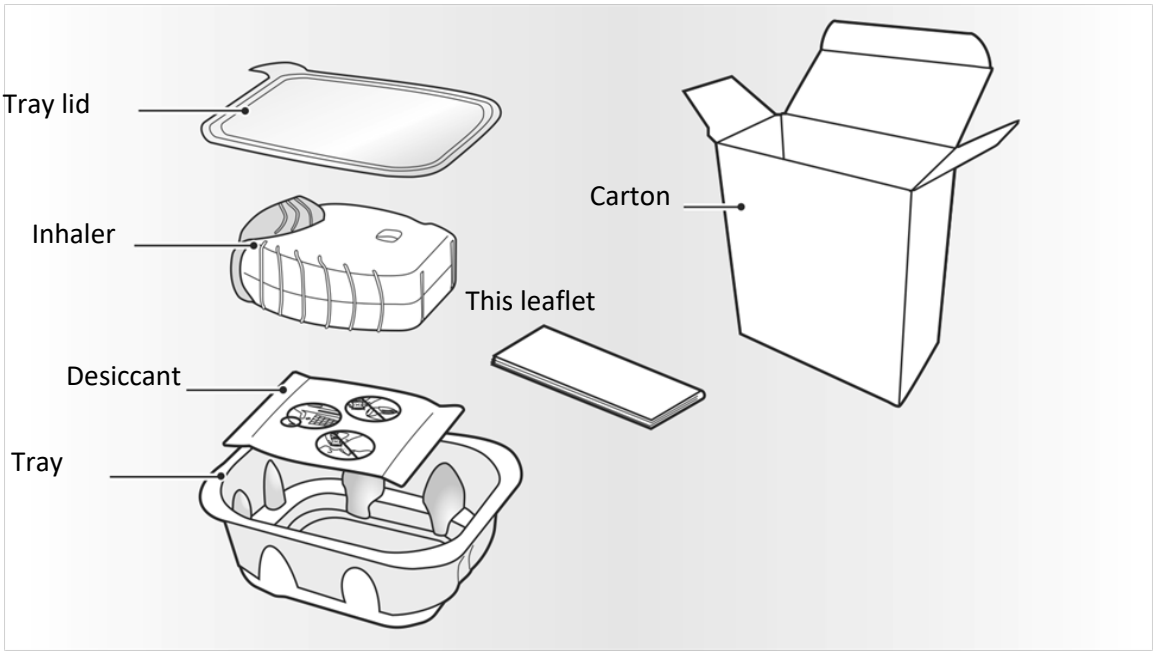
The plastic Ellipta inhaler consists of a light grey body, a red mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

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.

6.6 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** 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 date you open the tray. **After this date, the inhaler should no longer be used.**

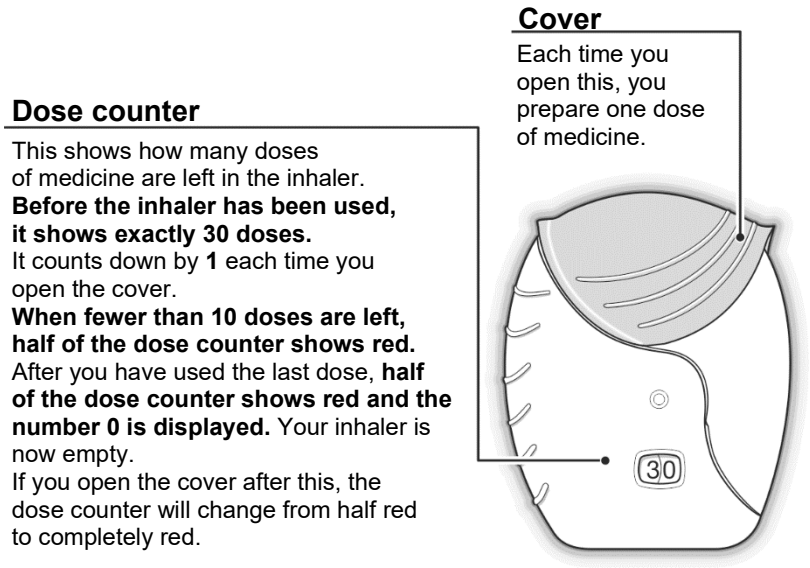
The step-by-step instructions shown below for the 30-dose (30 day supply) Ellipta inhaler also apply to the 7-dose (7 day supply) Ellipta inhaler.

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.

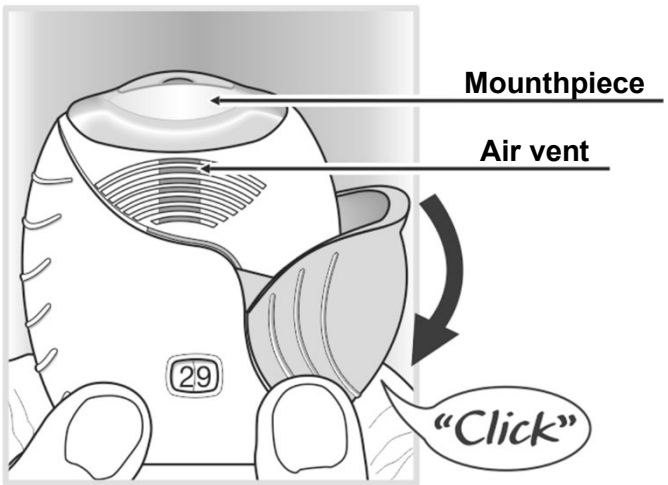
It is not possible to accidentally take extra medicine or a double dose in one inhalation.



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.**

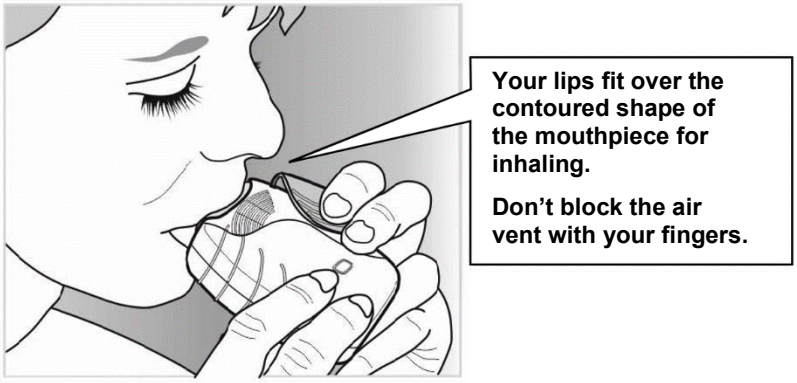
c) Inhale your medication

- **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).**

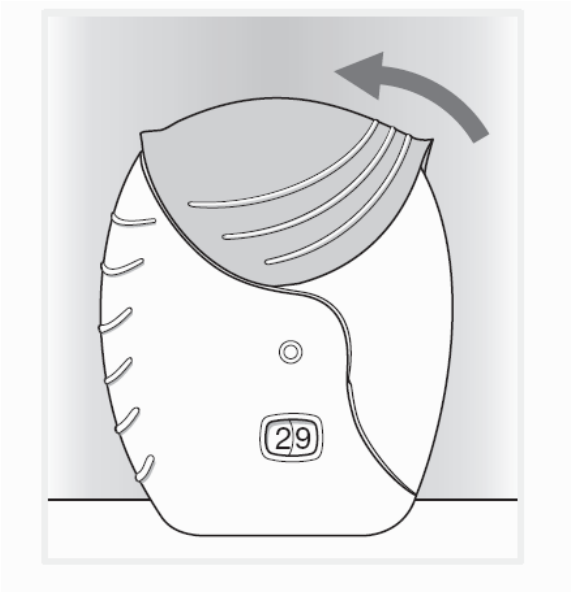
- **Remove the inhaler from your mouth.**

- **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.

7. Marketing authorization Holder

GlaxoSmithKline (Thailand) Ltd.

8. Marketing Authorization Number

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9. Date of authorization

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