# ANORO ELLIPTA

## Umeclidinium/vilanterol

## 1. NAME OF THE MEDICINAL PRODUCT

ANORO ELLIPTA

## 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. Therapeutic indications

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

### 4.2. Posology and method of 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. Special warnings and precautions for use

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. Interaction with other medicinal products and other forms of interaction

### Interaction with beta-blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-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. Fertility, 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

Pregnancy Category C: 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 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 *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. Undesirable effects

### Clinical trial data

The safety profile of *ANORO ELLIPTA* is based on approximately 3000 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 1600 patients who received 62.5/25 micrograms and approximately 1300 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**<br>**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 |
| Cardiac Disorders | Atrial Fibrillation | Uncommon |
| | Supraventricular tachycardia | Uncommon |
| | Tachycardia | Uncommon |
| Respiratory, Thoracic and Mediastinal Disorders | Cough | Common |
| | Oropharyngeal pain | Common |
| Gastrointestinal Disorders | Constipation | Common |
| | Dry mouth | Common |

### Post-marketing data

| MedDRA<br>System organ class | Adverse reaction(s) | Frequency |
|---|---|---|

| | | |
|---|---|---|
| Immune system disorders | Hypersensitivity reactions including:<br>Rash<br>Anaphylaxis, angioedema, and urticaria | <br>Uncommon<br>Rare |
| Psychiatric disorders | Anxiety | Uncommon |
| Nervous system disorders | Tremor<br>Dysgeusia | Uncommon<br>Uncommon |
| Eye disorders | Vision blurred<br>Glaucoma<br>Intraocular pressure increased | Rare<br>Rare<br>Rare |
| Cardiac disorders | Palpitations | Uncommon |
| Respiratory, Thoracic and Mediastinal Disorders | Paradoxical bronchospasm<br>Dysphonia | Rare<br>Rare |
| Musculoskeletal and connective tissue disorders | Muscle spasms | Uncommon |
| Renal and urinary disorders | Urinary retention<br>Dysuria | Rare<br>Rare |

## To report any side effect(s):

***Kingdom of Saudi Arabia***

**-National Pharmacovigilance centre (NPC)**

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2340
- Reporting hotline: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

**-GlaxoSmithKline - Head Office, Jeddah**

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: sa.aermi-saudi@gsk.com
- website: https://healthksa.gsk.com/

- P.O. Box 55850, Jeddah 21544, Saudi Arabia

### 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 beta$_2$-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 beta$_2$-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, 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 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 $beta_1$- 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

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 ≥1 unit 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 resulted in a statistically significant 50% reduction in risk of a moderate/severe COPD exacerbation (based on analysis of time to first exacerbation) compared with placebo (Hazard Ratio 0.5; 95% CI: 0.3, 0.8; p=0.004) where the majority of patients reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (72%) and no COPD exacerbations requiring hospitalisation (89%) in the 12 months prior to screening.

### 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 resulted in a statistically significant 50% reduction in risk of a moderate/severe COPD exacerbation (based on analysis of time to first exacerbation) compared with tiotropium (Hazard Ratio 0.5; 95% CI: 0.3, 1.0; p=0.044) where the majority of patients reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (83%) and no COPD exacerbations requiring hospitalisation (93%) in the 12 months prior to screening.

### 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).

## Supporting efficacy studies

In a randomised, double-blind, 52-week study (CTT116855, IMPACT), adult patients with COPD and a history of 1 or more moderate or severe exacerbations in the prior 12 months were randomised (1:2:2) to receive ANORO ELLIPTA 62.5/25 micrograms, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI 100/62.5/25 micrograms), or fluticasone furoate/vilanterol (FF/VI 100/25 micrograms) administered once daily. 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 ANORO ELLIPTA. The mean annual rate of exacerbations was 0.91, 1.07 and 1.21 for FF/UMEC/VI, FF/VI, and ANORO ELLIPTA respectively.

Treatment with ANORO ELLIPTA resulted in a similar risk of a moderate/severe exacerbation when compared with FF/VI (based on analysis of time to first exacerbation) (risk increase of +1.4%; Hazard Ratio:1.01; 95% CI: 0.94, 1.09; p=0.708).

### Umeclidinium

In the IMPACT study, treatment with umeclidinium as a component of FF/UMEC/VI compared with FF/VI resulted in a statistically significant 15% reduction in the annual rate of on-treatment moderate/severe exacerbations (Rate Ratio: 0.85; 95% CI: 0.80, 0.90; p<0.001).

Treatment with umeclidinium as a component of FF/UMEC/VI compared with FF/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).

### Vilanterol

In a placebo controlled study (HZC113782, SUMMIT), where patients with COPD were treated for up to 4 years (mean 1.7 years), the majority of patients reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (68%) and no COPD exacerbations requiring hospitalisation (87%) in the 12 months prior to screening. Treatment with vilanterol 25 micrograms resulted in a statistically significant 10% reduction in the annual rate of on-treatment moderate/severe exacerbations compared with placebo (Rate Ratio: 0.90; 95% CI: 0.82, 0.98; p=0.017). Vilanterol as a component of fluticasone furoate/vilanterol (FF/VI 100/25 micrograms) compared with fluticasone furoate (FF 100 micrograms) resulted in a statistically significant 19% reduction in the annual rate of on-treatment moderate/severe exacerbations (Rate Ratio: 0.81; 95% CI: 0.74, 0.88; p<0.001).

These findings were supported by a statistically significant 8.9% reduction in risk of a moderate/severe exacerbation (based on analysis of time to first exacerbation) for vilanterol compared with placebo (Hazard Ratio: 0.91; 95% CI: 0.84, 0.99; p=0.023) and by a statistically significant 18.2% reduction in risk of a moderate/severe exacerbation

(based on analysis of time to first exacerbation) for vilanterol as a component of FF/VI compared with FF (Hazard Ratio: 0.82; 95% CI: 0.75, 0.89; p<0.001).

### 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 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 ≥ 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 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 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 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 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

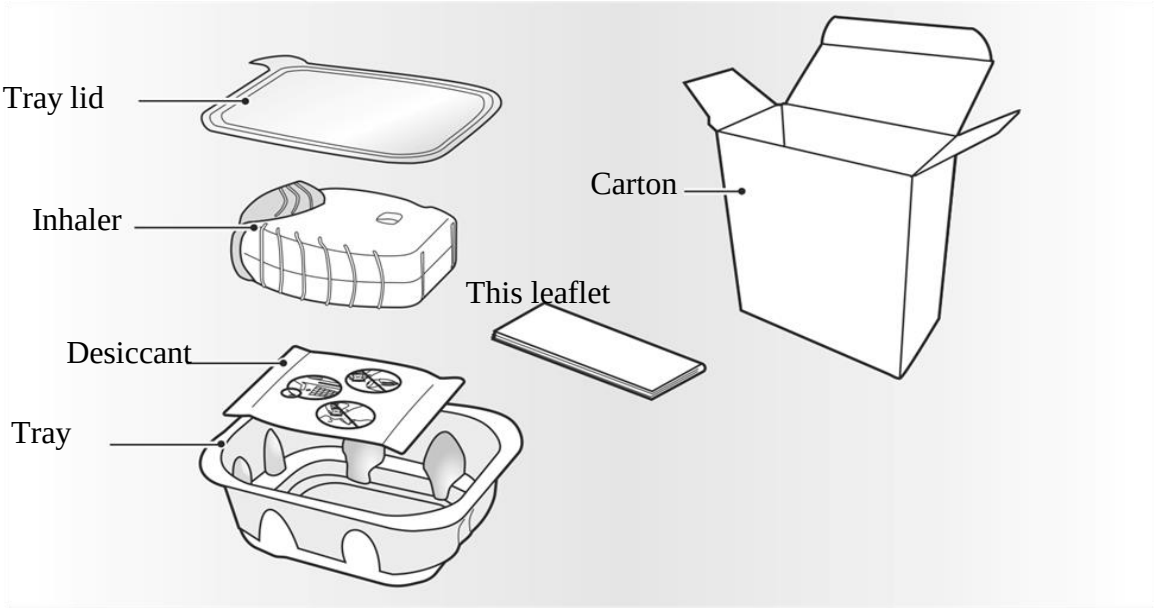
The plastic Ellipta inhaler consists of a light grey body, a red mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

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

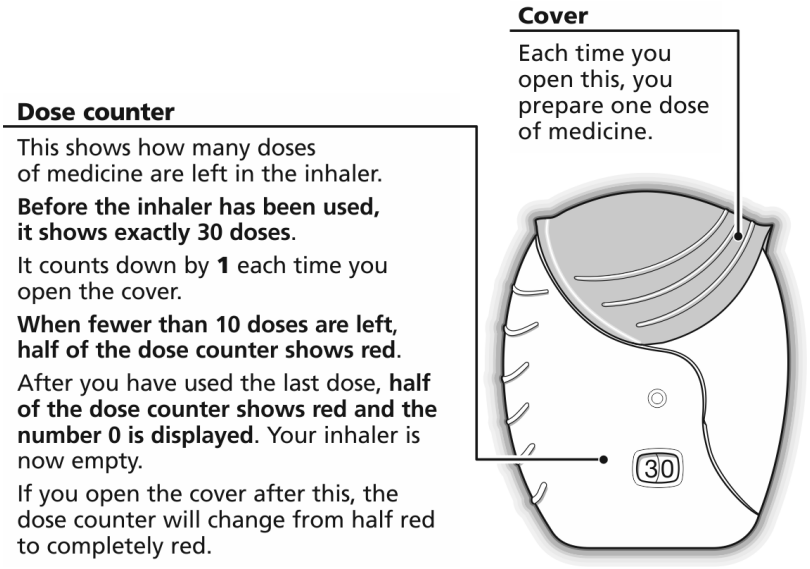
The step-by-step instructions shown below for the 30-dose (30 day supply) Ellipta inhaler also apply to the 7-dose (7 day supply) Ellipta inhaler.

### 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.

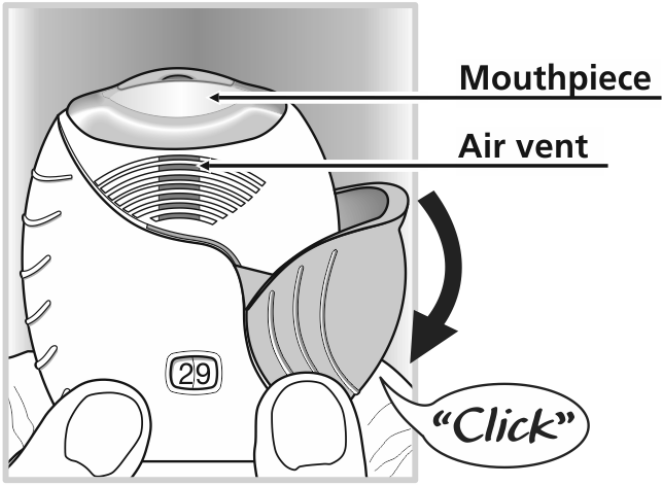
It is not possible to accidentally take extra medicine or a double dose in one inhalation.




### 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.

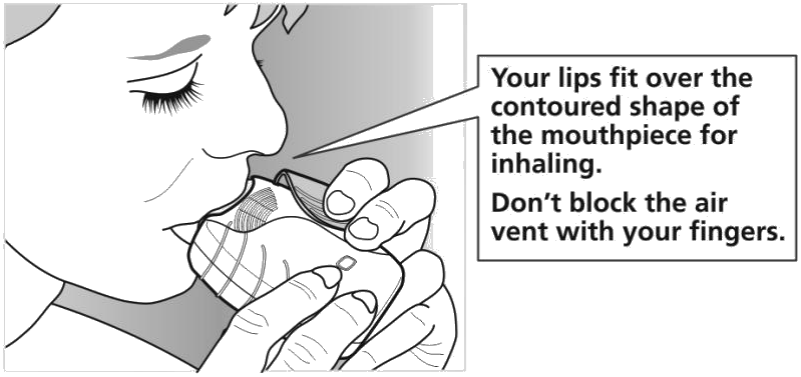
- If the dose counter does not count down as you hear the "click", the inhaler will not deliver medicine.
  Take it back to your pharmacist for advice.

- 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).

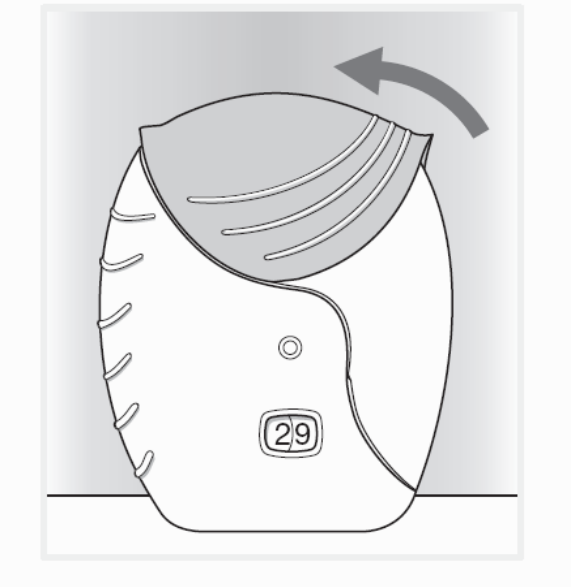
- Remove the inhaler from your mouth.

- 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.

**Version number: GDS07/IPI08**
**Date of issue: *19 Jul 2018***

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