## **ANORO**™ ELLIPTA™

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 65 micrograms

umeclidinium bromide equivalent to 55 micrograms of umeclidinium and 22 micrograms of vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate).

Excipient with known effect: Each delivered dose contains approximately 25 mg of lactose (as monohydrate). For the full list of excipients, see List of Excipients

PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed (inhalation powder).

White powder in a light grey inhaler (ELLIPTA) with a red mouthpiece cover and a dose counter. CLINICAL PARTICULARS

Therapeutic indications

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

## Posology and method of administration

# <u>Posology</u>

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

No dosage adjustment is required in patients over 65 years.

Renal impairment

No dosage adjustment is required in patients with renal impairment.

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

## Paediatric population

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

Method of administration ANORO ELLIPTA is for inhalation use only.

Instructions for use:

The following instructions for the 30 dose inhaler also apply to the 7 dose inhaler.

The ELLIPTA inhaler contains pre-dispensed doses and is ready to use. The inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. The desiccant sachet should

be thrown away and it should not be eaten or inhaled. The inhaler will be in the 'closed' position when it is first taken out of its sealed tray. It should not be opened until it is ready to be inhaled. The inhaler does not need to be stored in the foil laminate tray once it has been opened.

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

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

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

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

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

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

• Inhale with one long, steady, deep breath in. This breath should be held in for as long as possible (at least

3-4 seconds).

 Remove the inhaler from the mouth. Breathe out slowly and gently.

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

The mouthpiece of the inhaler may be cleaned using a dry tissue before closing the cover. Slide the cover upwards as far as it will go, to cover the mouthpiece.

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

**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, may be 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

# 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/vilanterol combination, 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**

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 Non-clinical information).

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 Non-clinical information). 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<sub>2</sub>-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.

Ability to perform tasks that require Judgement, Motor or Cognitive Skills There have been no studies to investigate the effect of ANORO ELLIPTA on the ability to perform tasks that

# require judgement, motor or cognitive skills.

#### **Adverse Reactions** 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. The following

convention has been used for the classification of adverse reactions:

Very common: ≥1/10 ≥1/100 to <1/10 Common: ≥1/1000 to <1/100 Uncommon:

≥1/10000 to <1/1000 <1/10000 Very rare

<u>MedDRA</u> 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

### Overdosage

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).

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,

## Clinical Pharmacolog

## Pharmacodynamics

Pharmacotherapeutic group: Drugs for obstructive airway diseases, adrenergics in combination with

#### anticholinergics ATC Code: R03AL03

Mechanism of action Umeclidinium/vilanterol is a combination inhaled long-acting muscarinic receptor antagonist/long-acting beta<sub>2</sub>-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 holinergic 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 is a selective long-acting, beta<sub>2</sub>-adrenergic receptor agonist (beta<sub>2</sub>-agonist).

The pharmacologic effects of beta<sub>2</sub>-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

Pharmacodynamic effects In one placebo controlled clinical efficacy study umeclidinium/vilanterol increased FEV<sub>1</sub> 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<sub>1</sub> during 0-6 hours post-dose at Day 1 and Week 24 was 0.27 L and 0.32 L respectively for umeclidinium/vilanterol, compared with 0.11 L (Day 1) and 0.10 L (Week 24)

#### 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.

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.

# Umeclidinium

Following inhaled administration of umeclidinium in healthy volunteers, C<sub>max</sub> 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.

Following inhaled administration of vilanterol in healthy volunteers, C<sub>max</sub> 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

## 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%.

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%.

n vitro studies showed that umeclidinium is metabolised principally by the enzyme P450 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.

*In vitro* studies showed that vilanterol is metabolised principally via 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<sub>1</sub>- and beta<sub>2</sub>- 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

Drug-drug interactions Available pharmacokinetic data in healthy volunteers and patients with COPD show that the systemic exposure ax and AUC) and population pharmacokinetic predicted exposures to umeclidinium and vilanterol is unaffected by administration with the umeclidinium/vilanterol combination compared to the components

Co-administration with the strong CYP3A4 inhibitor ketoconazole (400 mg) increased mean vilanterol AUC<sub>(0-t)</sub> and C<sub>max</sub> 65% and 22% respectively. The increase in vilanterol exposure was not associated with an increase beta-agonist related systemic effects on heart rate, blood potassium or QT interval (corrected using the

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<sub>max</sub>. 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.

Plasma clearance of vilanterol following intravenous administration was 108 litres/hour. Following oral ministration 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

Hepatic impairment

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.

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

Subjects with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either

#### umeclidinium or vilanterol (C<sub>max</sub> and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. ANORO ELLIPTA 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

The safety and efficacy of umeclidinium/vilanterol 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 umeclidinium/vilanterol 62.5/25 micrograms and/or 125/25 micrograms, all once daily. Efficacy results for umeclidinium/vilanterol 62.5/25 micrograms are presented below.

### Placebo Controlled Studies

In one 6-month study, DB2113373, umeclidinium/vilanterol 62.5/25 micrograms demonstrated a statistically significant improvement in lung function (as defined by change from baseline trough FEV<sub>1</sub> at Week 24) compared with placebo (see Table 1). Bronchodilatory effects with umeclidinium/vilanterol compared with placebo were evident after the first day of treatment and were maintained over the 24 week treatment period.

		Trough FEV <sub>1</sub> (L)			
			Difference from Placebo		
	Baseline (SD)	Change from baseline (SE)	Treatment Difference (95% CI) p-value		
Study DB2113373					
Umeclidinium/vilanterol 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<sub>1</sub>= forced expiratory volume in 1 second; L= litres; mcg= micrograms; n= number receiving treatment; OD= once daily; SD= standard deviation; SE= standard error. Umeclidinium/vilanterol demonstrated a statistically significant greater improvement from baseline in weighted mean FEV<sub>1</sub> 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 umeclidinium/vilanterol (1.2 units; p<0.001). The percentage of patients receiving umeclidinium/vilanterol 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 umeclidinium/vilanterol (-5.51 units; p≤0.001). The percentage of patients receiving umeclidinium/ vilanterol 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 umeclidinium/vilanterol required less rescue salbutamol than those treated

needed (on average 36.1%) compared with placebo (on average 21.7%; no formal statistical analysis was performed on this endpoint) Treatment with umeclidinium/vilanterol 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

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 umeclidinium/vilanterol had more days when no rescue medication was

# reduction 50%, p=0.004). **Tiotropium Comparator Studies**

In studies ZEP117115 and DB2113360, treatment with umeclidinium/vilanterol 62.5/25 micrograms provided statistically significant and clinically meaningful improvements in change from baseline in trough FEV<sub>1</sub> compared with tiotropium at Week 24 (see *Table 2*). In Study DB2113374, umeclidinium/vilanterol 62.5/25 micrograms showed a clinically meaningful improvement in change from baseline in trough FEV<sub>1</sub> compared with tiotropium at Week 24 (see *Table 2*).

# Table 2. Primary efficacy endpoint at Week 24 (Studies ZEP117115, DB2113360 and DB2113374) Trough FEV<sub>1</sub> (L)

			Difference from tiotropium
	Baseline (SD)	Change from baseline (SE)	Treatment Difference (95% CI) p-value
Study ZEP117115			
Umeclidinium/ vilanterol 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			
Umeclidinium/ vilanterol 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/ vilanterol 62.5/25 mcg OD (n=217)	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<sub>1</sub>= 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

In Studies ZEP117115 and DB2113360 umeclidinium/vilanterol showed statistically significant greater improvements of 0.11 L and 0.07 L respectively in change from baseline in weighted mean FEV<sub>1</sub> over 0-6 hours at Week 24 compared with tiotropium (both p≤0.005). In Study DB2113374 umeclidinium/vilanterol showed a clinically meaningful improvement of 0.10 L in change from baseline in weighted mean FEV<sub>1</sub> over 0-6 hours at Week 24 compared with tiotropium.

ficance cannot be inferred for this comparison.

NON-CLINICAL INFORMATION

In Studies DB2113360 and DB2113374, umeclidinium/vilanterol 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 umeclidinium/vilanterol (-2.10 units; p=0.006). The percentage of patients receiving umeclidinium/ vilanterol 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 umeclidinium/vilanterol over tiotropium in studies ZEP117115 (-0.5 puffs per day; p<0.001) and DB2113360

Throughout studies ZEP117115, DB2113360 and DB2113374, patients treated with umeclidinium/vilanterol 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 umeclidinium/vilanterol 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 umeclidinium/vilanterol 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 umeclidini vilanterol 62.5/25 micrograms did not show a statistically significant improvement over placebo in EET (21.9 seconds: p>0.05).

In Study DB2114418, umeclidinium/vilanterol showed a statistically significant improvement compared to placebo in change from baseline in trough FEV<sub>1</sub> 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, umeclidinium/vilanterol showed a clinically meaningful improvement compared to placebo in change from baseline in trough FEV<sub>1</sub> 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).

In nonclinical studies with umeclidinium and vilanterol, findings were those typically associated with the primary pharmacology of either muscarinic receptor antagonists or beta<sub>2</sub>-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

Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures  $\geq$  26 or  $\geq$  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<sub>2</sub>-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<sub>2</sub>-agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation) at 6-times the human clinical exposure based on AUC. When given subcutaneously there were no effects at 36-times the human clinical exposure of 25 micrograms vilanterol based on AUC.

PHARMACEUTICAL PARTICULARS

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

Magnesium stearate Special Precautions for Storage Do not store above 30°C.

Following removal from the tray, the product may be stored for a maximum period of 6 weeks. Nature and Contents of Containe

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. The inhaler contains two strips of 30 regularly distributed blisters, each containing a white powder.

#### **GDS Version Number: 03** Version Date: 11 April 2014

Manufactured by:

In-use shelf-life:

Glaxo Operations UK Limited\*, Ware, Hertfordshire, UK.

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THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the

The doctor and the pharmacist are the experts in medicines, their benefits and risks. Do not by yourself interrupt the period of treatment prescribed.

Do not repeat the same prescription without consulting your doctor. Keep all medicaments out of the reach of children.

Council of Arab Health Ministers. Union of Arab Pharmacists.

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

When you take the inhaler out of the sealed tray, it will be in the 'closed' position. Don't open it until you are

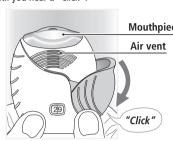
If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be securely held inside the inhaler, but it will no longer be available.

> Each time you open this, you This shows how many doses of prepare one dose medicine are left in the inhaler. of medicine. Before the inhaler has been used, it shows exactly 30 doses. It counts down by **1** each time you When fewer than 10 doses are left, half of the dose counter After you have used the last dose, half of the dose counter shows red and the number 0 is displayed. Your inhaler is now If you open the cover after this, the dose counter will change from half

# b) Prepare a dose

Wait to open the cover until you are ready to take your dose.

red to completely red.



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.

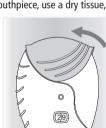
Take it back to your pharmacist for advice. Do not shake the inhaler at any time.

c) Inhale your medication

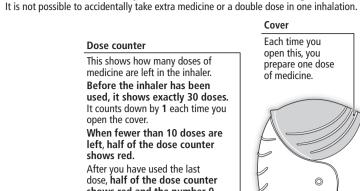
• While holding the inhaler away from your mouth, breathe out as far as is comfortable. Don't breathe out into the inhaler.

• Put the mouthpiece between your lips, and close your lips firmly around it.

- Don't block the air vent with your fingers Your lips fit over the contoured shape of the mouthpiece for inhaling 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.



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



When you first use the Ellipta inhaler you do not need to check that it is working properly, and you do not need

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

Dose counter

open the cover.

shows red.

a) Read this before you start

Do not shake the inhaler. • Slide the cover fully down until you hear a "click".

