TRELEGY ELLIPTA

Fluticasone furoate/umeclidinium/vilanterol

1. NAME OF THE MEDICINAL PRODUCT

TRELEGY ELLIPTA
Fluticasone furoate/umeclidinium/vilanterol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 62.5 micrograms umeclidinium (equivalent to 74.2 micrograms umeclidinium bromide) and 25 micrograms vilanterol (as trifenatate). Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 92 micrograms fluticasone furoate, 55 micrograms umeclidinium (equivalent to 65 micrograms umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate).

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed
White powder for inhalation packed in blister strip of ***Ellipta*** inhaler

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Trelegy Ellipta is indicated for the maintenance treatment of adults with moderate to severe COPD who require treatment with combination of a long-acting muscarinic antagonist, a long-acting beta$_2$-agonist and an inhaled corticosteroid.

Trelegy Ellipta is not indicated for the initiation of therapy in COPD.

Important Limitations of Use

Trelegy Ellipta is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

4.2 Posology and Method of Administration

Trelegy Ellipta is for oral inhalation only.

After inhalation, the patient should rinse their mouth with water without swallowing.

Adults

The recommended and maximum dose is one inhalation of ***Trelegy Ellipta*** 100/62.5/25

micrograms once daily, at the same time each day.

Children and adolescents
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 *Pharmacokinetic Properties – Special Patient Populations*).
Renal impairment
No dosage adjustment is required for patients with renal impairment (see *Pharmacokinetic Properties – Special Patient Populations*).

Hepatic Impairment
Trelegy Ellipta should be used with caution in patients with severe hepatic impairment. Umeclidinium has not been studied in patients with severe hepatic impairment (see *Special Warnings and Special Precautions for Use, Pharmacokinetic Properties — Special Patient Populations*).

4.3 Contraindications

Trelegy Ellipta is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to fluticasone furoate, umeclidinium, vilanterol or any of the excipients.

4.4 Special Warnings and Special Precautions for Use

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

Exacerbations

Trelegy 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.

Patients should not stop therapy with ***Trelegy Ellipta*** without physician supervision since symptoms may recur after discontinuation.

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing, and may be life-threatening. Treatment with ***Trelegy Ellipta*** should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists or sympathomimetic agents, including umeclidinium or vilanterol, respectively. Therefore, ***Trelegy Ellipta*** should be used with caution in patients with unstable or life-threatening cardiovascular disease.

Patients with hepatic impairment

Patients with moderate to severe hepatic impairment receiving ***Trelegy Ellipta*** should be monitored for systemic corticosteroid-related adverse reactions (see *Pharmacokinetic Properties – Special Patient Population*).

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include hypothalamic-pituitary-adrenal (HPA) suppression, decrease in bone mineral density, cataract, glaucoma, and central serous chorioretinopathy (CSCR).

As with all medication containing corticosteroids, ***Trelegy Ellipta*** should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Antimuscarinic activity

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

Pneumonia

In line with the known class effect of inhaled corticosteroids, pneumonia events (including pneumonias resulting in hospitalisation) were observed in patients with COPD receiving ***Trelegy Ellipta***. In some instances, fatal events of pneumonia have been reported with use of inhaled corticosteroid fluticasone furoate-containing drugs, including ***Trelegy Ellipta*** (see *Undesirable Effect*). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving inhaled corticosteroid-containing drugs include current smokers, patients with a history of prior pneumonia, patients with low body mass index and patients with severe COPD. These factors should be considered when ***Trelegy Ellipta*** is prescribed, and treatment should be re-evaluated if pneumonia occurs.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Clinically significant drug interactions mediated by fluticasone furoate, umeclidinium or vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists, such as vilanterol. If beta-blockers are required, cardioselective beta-blockers should be considered; however, caution should be exercised during concurrent use of both non-selective and selective beta-blockers.

Interaction with CYP3A4 inhibitors
Fluticasone furoate and vilanterol, both components of ***Trelegy Ellipta***, are rapidly cleared by extensive first-pass metabolism mediated by the enzyme CYP3A4.

Care is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see *Pharmacokinetic Properties*).

Interaction with monoamine oxidase inhibitors and tricyclic antidepressants
Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Other long acting antimuscarinics and long acting beta$_2$- adrenergic agonists
Co-administration of ***Trelegy Ellipta*** with other long-acting muscarinic antagonists or long-acting beta$_2$- adrenergic agonists has not been studied and is not recommended as it may potentiate the adverse reactions (see *Undesirable Effect and Overdose*).

Hypokalaemia
Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of beta$_2$-adrenergic agonists, therefore caution should be exercised.

4.6 Use During Pregnancy and Lactation

Fertility
There are no data on the effects of ***Trelegy Ellipta*** on human fertility. Animal studies indicate no effects on male or female fertility *(*see *Pre-clinical Safety Data).*

Use in Pregnancy
There are insufficient data from the use of ***Trelegy Ellipta*** in pregnant women. Animal studies have shown reproductive toxicity after administration of beta$_2$-agonists or corticosteroids (see *Pre-clinical Safety Data*).

Trelegy Ellipta should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Use in Lactation
It is unknown whether fluticasone furoate, umeclidinium, vilanterol or their metabolites are excreted in human milk. However, other corticosteroids, muscarinic antagonists and beta$_2$-agonists are detected in human milk. A risk to breast-fed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue ***Trelegy Ellipta*** therapy taking into account the benefit of breast-feeding 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 ***Trelegy Ellipta*** on the ability to perform tasks that require judgement, motor or cognitive skills.

A detrimental effect on such activities would not be anticipated from the pharmacology of fluticasone furoate, umeclidinium or vilanterol at clinical doses.

4.8 Undesirable Effects

Clinical trial data

The safety profile of ***Trelegy Ellipta*** is based on three phase III clinical studies.

The first study included safety data from 911 patients with COPD who received doses of ***Trelegy Ellipta*** 100/62.5/25 micrograms once daily for up to 24 weeks, of whom 210 patients received ***Trelegy Ellipta*** 100/62.5/25 micrograms once daily for up to 52 weeks, with an active comparator (study CTT116853, FULFIL).

The second study included safety data from 527 patients with COPD who received ***Trelegy Ellipta*** 100/62.5/25 micrograms and 528 patients with COPD who received fluticasone furoate/vilanterol 100/25 micrograms + umeclidinium 62.5 micrograms once daily for up to 24 weeks (study 200812).

The third study included safety data from 4,151 patients with COPD who received ***Trelegy Ellipta*** 100/62.5/25 micrograms once daily for up to 52 weeks, with two active comparators (study CTT116855, IMPACT).

Where adverse reaction frequencies differed between studies, the higher frequency is reported below.

Adverse reactions are listed below by MedDRA system organ class and by frequency (*Table 1*). The following convention has been used for the classification of adverse reactions:

Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1,000 to <1/100
Rare: ≥1/10,000 to <1/1,000
Very rare: <1/10,000

Table 1. Adverse Reactions

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Nasopharyngitis	Very common

	Pneumonia* Upper respiratory tract infection Bronchitis Pharyngitis Rhinitis Sinusitis Influenza Candidiasis of mouth and throat Urinary tract infection Viral respiratory tract infection	Common
Nervous system disorders	Headache	Common
	Dysgeusia	Uncommon
Cardiac disorders	Supraventricular tachyarrhythmia Tachycardia Atrial fibrillation	Uncommon
Respiratory, thoracic & mediastinal disorders	Cough Oropharyngeal pain	Common
	Dysphonia	Common
Gastrointestinal disorders	Constipation	Common
	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia Back pain	Common
	Fractures	Uncommon

Description of selected adverse reactions

*Pneumonia (see *Special Warnings and Special Precautions for Use*)

In a total of 1,810 patients with advanced COPD (mean post-bronchodilator screening FEV_1 45% of predicted, standard deviation [SD] 13%), 65% of whom had experienced a moderate/severe COPD exacerbation in the year prior to study entry (study CTT116853), a higher incidence of pneumonia events was reported in patients receiving ***Trelegy Ellipta*** (20 patients, 2%) than in patients receiving budesonide/formoterol (7 patients, <1%). Pneumonia which required hospitalisation occurred in 1% of patients receiving ***Trelegy Ellipta*** and <1% of patients receiving budesonide/formoterol up to 24 weeks. One fatal case of pneumonia was reported in a patient who received ***Trelegy Ellipta***. In the subset of 430 patients treated for up to 52 weeks, the incidence of pneumonia events reported in the ***Trelegy Ellipta*** and budesonide/formoterol arms was equal at 2%.

In a 52-week study, a total of 10,355 patients with COPD with a history of 1 or more moderate or severe exacerbations within the prior 12 months (mean post-bronchodilator screening FEV_1 46% of predicted, SD 15%) (study CTT116855), the incidence of pneumonia was 8% for ***Trelegy Ellipta*** (n = 4,151), 7% for fluticasone furoate/vilanterol (n = 4,134), and 5% for umeclidinium/vilanterol (n = 2,070). Fatal pneumonia occurred in 12 of 4,151 patients (3.5 per 1,000 patient-years) receiving ***Trelegy Ellipta***, 5 of 4,134 patients (1.7 per 1,000 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (2.9 per 1,000 patient-years) receiving umeclidinium/vilanterol.

The incidence of pneumonia events with ***Trelegy Ellipta*** is comparable with that observed with fluticasone furoate/vilanterol 100/25 micrograms in clinical studies in COPD.

Post-marketing data

System organ class	Adverse reactions	Frequency
Immune system disorders	Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria and rash	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Rare
Psychiatric disorders	Anxiety	Rare
Nervous system disorders	Tremor	Rare
Eye disorders	Vision blurred, glaucoma, eye pain Intraocular pressure increased	Uncommon Rare
Cardiac disorders	Palpitations	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Rare
Renal and urinary disorders	Urinary retention, dysuria	Rare

4.9 Overdose

No data from clinical studies are available regarding overdose of ***Trelegy Ellipta***.

Symptoms and signs

An overdose of ***Trelegy Ellipta*** may produce signs, symptoms or adverse effects associated with the individual components' pharmacological actions (see *Special Warnings and Special Precautions for Use and Pharmacodynamic Properties*).

Treatment

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

Cardioselective beta-blockade should only be considered for profound vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

ATC code
Pharmacotherapeutic group: Drugs for obstructive airways diseases, Adrenergics in combination with anticholinergics including triple combinations with corticosteroids, ATC code: R03AL08.

Mechanism of action

Fluticasone furoate, umeclidinium and vilanterol represent three classes of medications: a synthetic corticosteroid, a long-acting muscarinic receptor antagonist (also referred to as a LAMA or as an anticholinergic) and a selective, long-acting beta$_2$-receptor agonist (LABA), respectively.

Fluticasone furoate
Fluticasone furoate is a corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation.

Umeclidinium
Umeclidinium is a long-acting pan-muscarinic receptor antagonist (also referred to as an anticholinergic). Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic cholinergic 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 LABA. The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, 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

Cardiovascular effects
The effect of ***Trelegy Ellipta*** on the QT interval has not been evaluated in a thorough QT (TQT) study. TQT studies for fluticasone furoate/vilanterol and umeclidinium/vilanterol did not show clinically relevant effects on QT interval at clinical doses of fluticasone furoate, umeclidinium and vilanterol (see below).

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, 6.4) milliseconds seen 10 minutes after administration with umeclidinium/vilanterol 125/25 micrograms and 8.2 (90% CI: 6.2, 10.2) milliseconds 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 at the umeclidinium/vilanterol 125/25 micrograms dose. 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.

The effect of fluticasone furoate/vilanterol on the QT interval was evaluated in a double-

blind, multiple-dose, placebo- and positive-controlled crossover study in 85 healthy volunteers. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 4.9 (7.5) milliseconds and 9.6 (12.2) milliseconds seen 30 minutes after dosing with fluticasone furoate/vilanterol 200/25 micrograms and fluticasone furoate/vilanterol 800/100 micrograms, respectively. A dose-dependent increase in heart rate was also observed. The maximum mean (95% upper confidence bound) difference in heart rate from placebo after baseline-correction was 7.8 (9.4) beats/min and 17.1 (18.7) beats/min seen 10 minutes after dosing with fluticasone furoate/vilanterol 200/25 micrograms and fluticasone furoate/vilanterol 800/100 micrograms, respectively.

No clinically relevant effects on the QTc interval were observed on review of centrally read ECGs from 911 subjects with COPD exposed to ***Trelegy Ellipta*** for up to 24 weeks, or in the subset of 210 subjects exposed for up to 52 weeks.

5.2 Pharmacokinetic Properties

When fluticasone furoate, umeclidinium, and vilanterol were administered in combination by the inhaled route from a single inhaler in healthy subjects, the pharmacokinetics of each component were similar to those observed when each active substance was administered either as fluticasone furoate/vilanterol combination, umeclidinium/vilanterol combination, or each component as monotherapy.

Population PK analyses for fluticasone furoate/umeclidinium/vilanterol were conducted using a combined PK dataset from three phase III studies in 821 COPD subjects. Systemic drug levels (steady-state C_{max} and AUC) of fluticasone furoate, umeclidinium and vilanterol following fluticasone furoate/umeclidinium/vilanterol in one inhaler (triple combination) were within the range of those observed following fluticasone furoate/vilanterol plus umeclidinium administered via two inhalers, dual combinations (fluticasone furoate/vilanterol and umeclidinium/vilanterol), as well as individual single inhalers (fluticasone furoate, umeclidinium, and vilanterol).

Absorption

Fluticasone furoate

Following inhaled administration of ***Trelegy Ellipta*** in healthy subjects, fluticasone furoate C_{max} occurred at 15 minutes. The absolute bioavailability of fluticasone furoate when administrated as fluticasone furoate/vilanterol by inhalation was on average 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung, with negligible contribution from oral absorption. Following repeat dosing of inhaled fluticasone furoate/vilanterol, steady state was achieved within 6 days with up to 1.6-fold accumulation.

Umeclidinium

Following inhaled administration of ***Trelegy Ellipta*** in healthy subjects, umeclidinium C_{max} occurred at 5 minutes. The absolute bioavailability of inhaled umeclidinium was on average 13%, 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 ***Trelegy Ellipta*** in healthy subjects, vilanterol C_{max} occurred at 7 minutes. The absolute bioavailability of inhaled vilanterol was on average 27%, with negligible contribution from oral absorption. Following repeat dosing of inhaled fluticasone furoate/vilanterol, steady state was achieved within 6 days with up to 1.5-fold accumulation.

Distribution
Fluticasone furoate
Following intravenous administration of fluticasone furoate to healthy subjects, the mean volume of distribution was 661 litres. *In vitro* plasma protein binding in human plasma was >99.6%.

Umeclidinium
Following intravenous administration of umeclidinium 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 of vilanterol 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
Fluticasone furoate
In vitro studies showed that fluticasone furoate is metabolised principally by CYP3A4 and is a substrate for the P-glycoprotein (P-gp) transporter. Fluticasone furoate is primarily metabolised through hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity. Systemic exposure to the metabolites is low.

Umeclidinium
In vitro studies showed that umeclidinium is metabolised principally by CYP2D6 and is a substrate for the P-gp 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 CYP3A4 and is a substrate for the P-gp 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
A repeat dose study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25 micrograms) and ketoconazole (400 milligrams, a strong CYP3A4 inhibitor and Pgp inhibitor). Co-administration increased mean fluticasone furoate $AUC_{(0-24)}$ and C_{max} by 36% and 33%, respectively. The increase in

fluticasone furoate exposure was associated with a 27% reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol $AUC_{(0-t)}$ and C_{max} by 65% and 22%, respectively. The increase in vilanterol exposure was not associated with an increase in beta-agonist related systemic effects on heart rate or blood potassium.

Fluticasone furoate, umeclidinium and vilanterol are substrates of P-gp. A repeat dose drug interaction study performed in healthy subjects who were administered with umeclidinium/vilanterol or umeclidinium, and the P-gp and moderate CYP3A4 inhibitor verapamil (240 milligrams), did not show any clinically significant effect on the pharmacokinetics of vilanterol or umeclidinium.

The effect of a CYP2D6 poor metaboliser genotype on the steady-state pharmacokinetics of umeclidinium was assessed in healthy volunteers (CYP2D6 normal metabolisers and CYP2D6 poor metabolisers). No clinically meaningful difference in systemic exposure to umeclidinium (500 micrograms which is eight-fold higher than the therapeutic dose) was observed following repeat daily inhaled dosing to normal and CYP2D6 poor metaboliser subjects.

Elimination

Fluticasone furoate

The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of fluticasone furoate/vilanterol was, on average, 24 hours. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Plasma clearance following intravenous administration was 65.4 litres/hour. Urinary excretion accounted for approximately 2% of the intravenously administered dose. Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine.

Umeclidinium

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 following intravenous administration was 151 litres/hour. Following intravenous administration, approximately 58% of the administered radiolabelled dose was excreted in faeces and approximately 22% of the administered radiolabelled dose was excreted in urine. The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration, 92% of the administered radiolabelled dose was excreted primarily in faeces. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration.

Vilanterol

Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours. Plasma clearance of vilanterol following intravenous administration was 108 litres/hour. Following oral administration of radiolabelled vilanterol, 70% of the radiolabel was excreted in urine and 30% in faeces. Primary elimination of vilanterol was by metabolism followed by excretion of metabolites in urine and faeces.

Special Patient Populations

In a population pharmacokinetic analysis (n = 821), the impact of demographic covariates (race/ethnicity, age, gender, weight) on the pharmacokinetics of fluticasone furoate,

umeclidinium, and vilanterol was evaluated. Renal and hepatic impairment were assessed in separate studies.

Race

In East Asian subjects with COPD (Japanese and East Asian Heritage) (n = 113) who received fluticasone furoate/umeclidinium/vilanterol, estimates of fluticasone furoate AUC_{ss} were on average 30% higher compared with Caucasian subjects. However, these higher systemic exposures are not expected to have a clinically relevant effect on 24 hour serum or urinary cortisol excretion. There was no effect of race on pharmacokinetics of umeclidinium or vilanterol in subjects with COPD.

No clinically relevant differences requiring dose adjustment based on race were observed in fluticasone furoate, umeclidinium or vilanterol systemic exposure.

Elderly

No clinically relevant effects requiring dose adjustment based on age were observed.

Renal impairment

Trelegy Ellipta has not been evaluated in subjects with renal impairment. However, studies have been conducted with fluticasone furoate/vilanterol and umeclidinium/vilanterol.

A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30 mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or $beta_2$-agonist systemic effects compared with healthy subjects.

A study in subjects with severe renal impairment administered with umeclidinium/vilanterol showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC). *In vitro* protein binding studies between subjects with severe renal impairment and healthy volunteers were conducted, and no clinically significant evidence of altered protein binding was seen.

The effects of haemodialysis have not been studied.

Hepatic Impairment

Trelegy Ellipta has not been evaluated in subjects with hepatic impairment. However, studies have been conducted with fluticasone furoate/vilanterol and umeclidinium/vilanterol.

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0–24)}$) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure (fluticasone furoate/vilanterol 200/25 micrograms) in subjects with moderate hepatic impairment (Child-Pugh B) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child-Pugh C) that received fluticasone furoate/vilanterol 100/12.5 micrograms there was no reduction in serum cortisol (10% increase in serum cortisol).

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was no significant increase in systemic exposure to vilanterol (C_{max} and AUC) in subjects with

mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C).

There were no clinically relevant effects of the fluticasone furoate/vilanterol combination on beta-adrenergic systemic effects (heart rate or serum potassium) in subjects with mild or moderate hepatic impairment (vilanterol, 25 micrograms) or with severe hepatic impairment (vilanterol, 12.5 micrograms) compared with healthy subjects.

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 by umeclidinium or decreased protein binding by vilanterol between subjects with moderate hepatic impairment and healthy volunteers was observed *in vitro*.

Umeclidinium has not been evaluated in subjects with severe hepatic impairment.

Other patient characteristics
No clinically relevant differences requiring dose adjustment based on the effect of gender, weight or body mass index were observed.

CYP2D6 poor metabolisers showed no evidence of a clinically significant effect of CYP2D6 genetic polymorphism on systemic exposure to umeclidinium.

Clinical Studies

Study 1
The efficacy of ***Trelegy Ellipta*** (FF/UMEC/VI 100/62.5/25 micrograms) administered as a once daily treatment in patients with a clinical diagnosis of COPD has been evaluated in one 24-week active-controlled study with an extension up to 52 weeks in a subset of patients (study CTT116853, FULFIL).

All patients were required to have a smoking history of at least 10 pack years; a post-salbutamol FEV_1/ FVC ratio <0.70; a clinical diagnosis of COPD, and a post-bronchodilator FEV_1 of <50% predicted normal or a post-bronchodilator FEV_1 <80% predicted normal and a history of ≥2 moderate exacerbations or one severe (hospitalised) exacerbation in the previous 12 months at screening. At screening, the mean post-bronchodilator FEV_1 was 45.5% predicted, and the mean reversibility was 8.17%. Approximately 55% of patients had a history of ≥2 moderate or ≥1 severe COPD exacerbations in the 12 months prior to screening.

Trelegy Ellipta 100/62.5/25 micrograms administered once daily demonstrated a statistically significant improvement in lung function (as defined by change from baseline trough FEV_1 at Week 24; co-primary endpoint) compared with budesonide/formoterol (BUD/FOR) 400/12 micrograms administered twice-daily (see *Table 2)*. Bronchodilatory effects with ***Trelegy Ellipta*** were evident on the first day of treatment and were maintained over the 24-week treatment period.

Trelegy Ellipta demonstrated a statistically significant improvement compared with BUD/FOR at Week 24 for Health Related Quality of Life (HRQoL) measured by the St. George's Respiratory Questionnaire (SGRQ) total score (co-primary endpoint), SGRQ responder analysis, COPD Assessment Test (CAT) score and CAT responder analysis, and also for respiratory symptoms measured using the Evaluating Respiratory Symptoms in COPD (E-RS^{TM}: COPD) score and sub-scale scores over Weeks 21-24, breathlessness measured using the Transitional Dyspnoea Index (TDI) focal score at Week 24, and rescue

medication use measured by mean number of occasions per day over Weeks 1-24 (see *Table 2*).

Trelegy Ellipta demonstrated a statistically significant reduction in the annual rate of moderate/severe exacerbations (i.e. requiring treatment with antibiotics or corticosteroids or hospitalisation; extrapolated from data up to Week 24) compared with BUD/FOR. A reduction in the risk of a moderate/severe exacerbation was observed with ***Trelegy Ellipta*** compared with BUD/FOR (based on analysis of the time to first exacerbation) (see *Table 2*).

Table 2. Key efficacy endpoints up to Week 24 (Study CTT116853)

	Trelegy Ellipta **FF/UMEC/VI 100/62.5/25 mcg OD (n= 911)**	**BUD/FOR 400/12 mcg BID (n=899)**	**Comparison with BUD/FOR**	
			Treatment Difference (95% CI) p-value	**Treatment Ratio (95% CI) p-value**
Trough FEV_1 (L) at Week 24, LS mean change from baseline (SE) [a, e]	0.142 (0.0083)	-0.029 (0.0085)	0.171 (0.148, 0.194) p<0.001	-
SGRQ Total Score at Week 24, LS mean change from baseline (SE) [a, f]	-6.6 (0.45)	-4.3 (0.46)	-2.2 (-3.5, -1.0) p<0.001	-
Responders according to SGRQ Total Score at Week 24, % [f, h]	50%	41%	-	1.41 [b] (1.16, 1.70) p<0.001
Annual rate of on-treatment moderate/severe COPD exacerbation (based on data up to Week 24)	0.22	0.34	-	0.65 [c] (0.49, 0.86) p=0.002
Incidence of moderate/severe COPD exacerbation up to Week 24, %	10%	14%	-	0.67 [d] (0.52, 0.88) p=0.004
E-RS: COPD Total Score during Weeks 21-24, LS mean change from baseline (SE) [g]	-2.31 (0.157)	-0.96 (0.160)	-1.35 (-1.79, -0.91) p<0.001	-
Responders according to E-RS: COPD Total Score during Weeks 21-24, % [g, h]	47%	37%	-	1.59 [b] (1.30, 1.94) p<0.001
TDI focal score at Week 24, LS mean (SE) [f]	2.29 (0.096)	1.72 (0.099)	0.57 (0.30, 0.84) p< 0.001	-
Responders according to TDI focal score at Week 24, % [f, h]	61%	51%	-	1.61 [b] (1.33, 1.95) p<0.001
Daily activity percentage of days with score of 2 (able to perform more activities than usual) over Weeks 1-24, LS mean change from baseline (SE)	0.0 (0.38)	-0.1 (0.39)	0.1 (-0.9, 1.1) p=0.817	-

Mean number of occasions of rescue medication use per day over Weeks 1-24, LS mean change from baseline (SE)	-0.1 (0.04)	0.1 (0.04)	-0.2 (-0.3, -0.1) p<0.001	-
CAT Score at Week 24, LS mean change from baseline (SE) [f]	-2.5 (0.18)	-1.6 (0.19)	-0.9 (-1.4, -0.4) p<0.001	-
Responders according to CAT Score at Week 24, %[h]	53%	45%	-	1.44 [b] (1.19, 1.75) p<0.001

BID=twice daily; BUD=budesonide; FOR=formoterol; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; L=litres; LS=least squared; mcg=micrograms; n=number in the intent-to-treat population; OD=once daily; SE=standard error; SGRQ=St. George's Respiratory Questionnaire; CAT=COPD Assessment Test; E-RS=Evaluating Respiratory Symptoms; TDI=Transitional Dyspnoea Index.

[a] Co-primary endpoints. [b] Odds ratio. [c] Rate ratio. [d] Hazard ratio based on analysis of time to first event.
[e] Statistically significant treatment difference for FF/UMEC/VI vs. BUD/FOR also observed at Weeks 2, 4 and 12.
[f] Statistically significant treatment difference for FF/UMEC/VI vs. BUD/FOR also observed at Week 4.
[g] Statistically significant treatment difference for FF/UMEC/VI vs. BUD/FOR also observed over each 4-weekly period during the study duration.
[h] Response was defined as a ≥4 unit decrease from baseline for SGRQ, a ≥2 unit decrease from baseline for E-RS total score and for CAT and a ≥1 unit score for TDI.

The lung function, HRQoL, symptoms and exacerbations outcomes up to 52 weeks of treatment in a subset of patients (n = 430) were consistent with the results up to 24 weeks.

Study 2

The long-term efficacy of ***Trelegy Ellipta*** (FF/UMEC/VI 100/62.5/25 micrograms) administered once daily in patients with COPD with a history of moderate or severe exacerbations within the prior 12 months has been evaluated in a 52-week, active-controlled study compared with the fixed-dose combination of fluticasone furoate/vilanterol (FF/VI 100/25 micrograms) and umeclidinium/vilanterol (UMEC/VI 62.5/25 micrograms) (randomization 2:2:1) (study CTT116855, IMPACT).

Patients treated with ***Trelegy Ellipta*** demonstrated a statistically significant reduction in the annual rate of on-treatment moderate/severe exacerbations (primary endpoint) compared with FF/VI and compared with UMEC/VI. See *Table 3* for efficacy endpoint results.

Table 3. Key efficacy endpoints (Study CTT116855)

	***Trelegy Ellipta* FF/UMEC/VI (n = 4,151)**	**FF/VI (n = 4,134)**	**UMEC/VI (n = 2,070)**	***Trelegy Ellipta* FF/UMEC/VI vs. FF/VI**	***Trelegy Ellipta* FF/UMEC/VI vs. UMEC/VI**
Rate of Moderate/severe exacerbations[a]					
Exacerbations per year	0.91	1.07	1.21		
Reduction in Rate (%) 95% CI p-value				15% 10, 20 p<0.001	25% 19, 30 p<0.001
Time to first moderate/severe exacerbation					
Patients with an event (%)	47%	49%	50%		

Reduction in Risk (%) 95% CI p-value				14.8% 9.3, 19.9 p<0.001	16.0% 9.4, 22.1 p<0.001
Rate of Severe exacerbations					
Exacerbations per year	0.13	0.15	0.19		
Reduction in Rate (%) 95% CI p-value				13% -1, 24 p=0.064	34% 22, 44 p<0.001
Trough FEV_1 (L) at Week 52					
LS mean change from baseline (SE)	0.094 (0.004)	-0.003 (0.004)	0.040 (0.006)		
Treatment difference 95% CI p-value				0.097 0.085, 0.109 p<0.001	0.054 0.039, 0.069 p<0.001
SGRQ Total Score at Week 52					
LS mean change from baseline (SE)	-5.5 (0.23)	-3.7 (0.24)	-3.7 (0.35)		
Treatment difference 95% CI p-value				-1.8 -2.4, -1.1 p<0.001	-1.8 -2.6, -1.0 p<0.001
Responders according to SGRQ Total Score at Week 52					
Responder[b] (%)	42%	34%	34%		
Odds Ratio 95% CI p-value				1.41 1.29, 1.55 p<0.001	1.41 1.26, 1.57 p<0.001

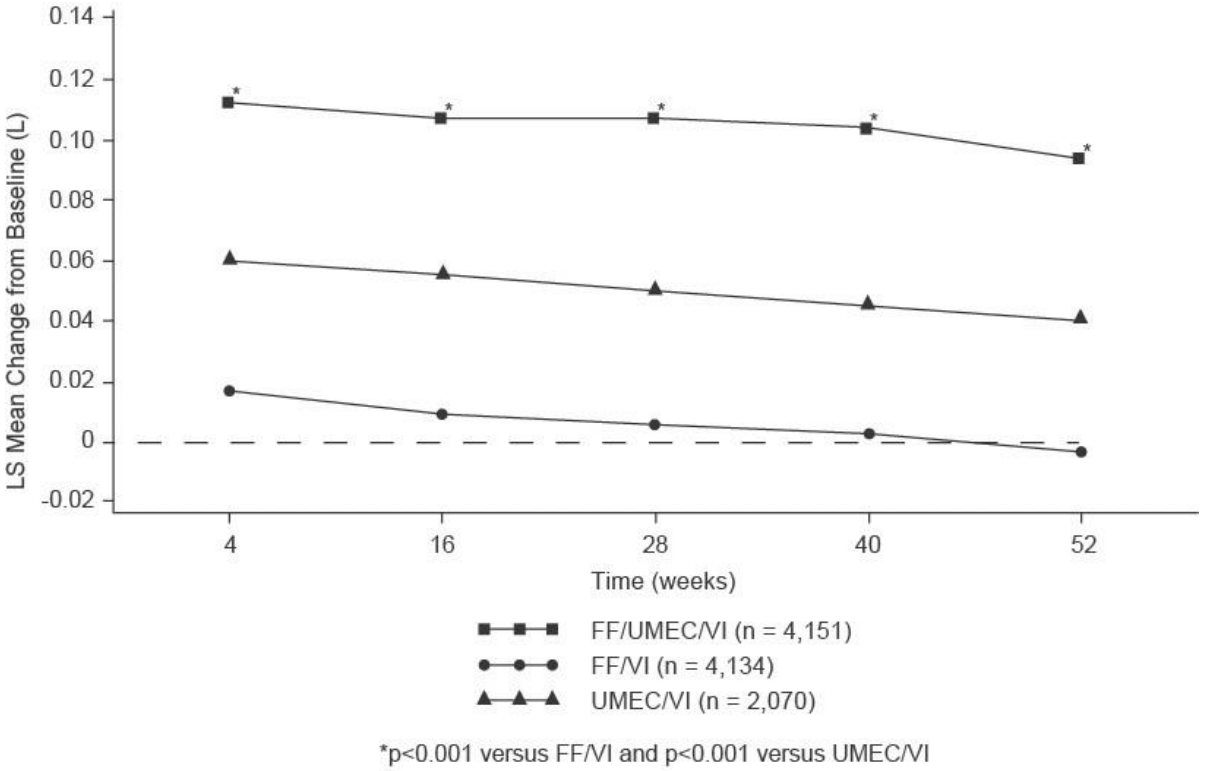
CI=confidence interval; FEV_1=forced expiratory volume in 1 second; L=litres; LS=least squared; n=number in the intent-to-treat population; SE=standard error; SGRQ=St. George's Respiratory Questionnaire.

[a] Primary endpoint.

[b] Defined as an SGRQ total score of 4 units below baseline or lower.

The effects on lung function (change from baseline trough FEV_1) of ***Trelegy Ellipta*** compared with FF/VI and UMEC/VI for trough FEV_1 were observed at all timepoints over the course of the 52-week study (see *Figure 1*).

Figure 1. Least Squares (LS) Mean Change from Baseline in Trough FEV_1 (L)



The reduction in the mean number of occasions/day of $beta_2$-agonist rescue medication use and the percentage of 24-hour periods without need of rescue medication was statistically significant in patients receiving ***Trelegy Ellipta*** compared with FF/VI or UMEC/VI at Weeks 49 to 52 (see *Table 4*) and these differences were observed over the course of the 52-week study.

Patients receiving ***Trelegy Ellipta*** had statistically significantly greater reduction in nighttime awakenings due to COPD symptoms compared with FF/VI or UMEC/VI at Weeks 49 to 52 (see *Table 4*) and these differences were observed over the course of the 52-week study for UMEC/VI and for the majority of timepoints for FF/VI.

Table 4. Other endpoints (Study CTT116855)

	***Trelegy Ellipta* FF/UMEC/VI (n = 4,151)**	**FF/VI (n = 4,134)**	**UMEC/VI (n = 2,070)**	***Trelegy Ellipta* FF/UMEC/VI vs. FF/VI**	***Trelegy Ellipta* FF/UMEC/VI vs. UMEC/VI**
Mean number of occasions/day of rescue medication use at Weeks 49 to 52					
LS mean change from baseline (SE)	0.16 (0.031)	0.44 (0.032)	0.46 (0.045)		
Treatment difference 95% CI p-value				-0.28 -0.37, -0.19 p<0.001	-0.30 -0.41, -0.19 p<0.001
Percentage of 24-hour periods without need of rescue medication at Weeks 49 to 52					
LS mean change from baseline (SE)	-1.9 (0.61)	-7.1 (0.62)	-6.3 (0.89)		

Treatment difference 95% CI p-value				5.2 3.5, 6.9 p<0.001	4.4 2.3, 6.5 p<0.001
Nighttime awakenings due to COPD symptoms at Weeks 49 to 52					
LS mean change from baseline (SE)	-0.21 (0.012)	-0.16 (0.013)	-0.12 (0.018)		
Treatment difference 95% CI p-value				-0.05 -0.08, -0.01 p=0.005	-0.10 -0.14, -0.05 p<0.001
CI=confidence interval; LS=least squared; n=number in the intent-to-treat population; SE=standard error.					

Treatment with ***Trelegy Ellipta*** demonstrated a clinically meaningful improvement of -2.0 points for COPD Assessment Test (CAT) score change from baseline at Week 52. Differences were statistically significant when compared with FF/VI (-0.5; 95% CI: -0.8, -0.2; p<0.001) and with UMEC/VI (-0.4; 95% CI: -0.8, -0.1; p=0.021).
The CAT responder rate (defined as 2 units below baseline or lower) at Week 52 was statistically significantly higher for patients treated with ***Trelegy Ellipta*** (42%) compared with FF/VI (37%; odds ratio 1.24; 95% CI: 1.14, 1.36; p<0.001) and with UMEC/VI (36%; odds ratio 1.28; 95% CI: 1.15, 1.43; p<0.001).

Breathlessness, measured using the Transitional Dyspnoea Index (TDI) focal score at Week 52, was measured in a subset of patients (N = 5,058 from 10 countries: Belgium, Canada, Czech Republic, Denmark, Germany, Netherlands, Poland, Spain, UK, USA). Treatment with ***Trelegy Ellipta*** (n = 2,029) demonstrated a statistically significant improvement compared with FF/VI (n = 2,014), LS mean TDI focal score of 0.98 and 0.71, respectively, a difference of 0.27 (95% CI: 0.04, 0.49; p=0.020). A statistically significant effect was not observed between ***Trelegy Ellipta*** and UMEC/VI (n = 1,015), LS mean TDI focal score of 0.98 and 0.89, respectively, a difference of 0.09 (95% CI: - 0.19, 0.37; p=0.522). The proportion of responders by TDI (defined as at least 1 unit) was statistically significantly higher for ***Trelegy Ellipta*** (36%) compared with FF/VI (29%; odds ratio 1.36; 95% CI: 1.19, 1.55; p<0.001) and UMEC/VI (30%; odds ratio 1.33; 95% CI: 1.13, 1.57; p<0.001) at Week 52.

Other supporting efficacy studies

Study 200812 was a 24-week, non-inferiority study (N = 1,055) that compared ***Trelegy Ellipta*** (FF/UMEC/VI 100/62.5/25 micrograms), administered as a single inhaler, with fluticasone furoate/vilanterol (100/25 micrograms) + umeclidinium (62.5 micrograms), co-administered as multi-inhaler therapy, once daily to patients with a history of moderate or severe exacerbations within the prior 12 months. In this study, FF/UMEC/VI was non-inferior compared with FF/VI + UMEC in the improvement from baseline in trough FEV_1 at week 24. The pre-specified non-inferiority margin was 50 mL.

<u>Umeclidinium with fluticasone furoate/vilanterol</u>

In two 12-week, placebo controlled studies (200109 and 200110), the addition of umeclidinium (62.5 micrograms) to fluticasone furoate/vilanterol (FF/VI) (100/25 micrograms) once daily in adult patients with a clinical diagnosis of COPD, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV1 at Day 85 compared with placebo plus FF/VI (124 mL [95% CI: 93, 154; p<0.001] in study 200109 and 122 mL [95% CI: 91,

152; p<0.001] in study 200110).

12-month studies with fluticasone furoate/vilanterol
Two 52-week randomised, double-blind, parallel-group studies (HZC102970 and HZC102871) compared the annual rate of moderate/severe exacerbations in adult patients with a clinical diagnosis of COPD, treated with FF/VI or with vilanterol once daily. The results of an integrated analysis of both studies showed that treatment with FF/VI 100/25 micrograms once daily resulted in a 27% reduction in the annual rate of moderate/severe COPD exacerbations compared with vilanterol (95% CI: 16, 37; p<0.001). Reductions in risk of moderate/severe exacerbation (based on analysis of time to first exacerbation) and rate of exacerbations requiring corticosteroid use were also observed with FF/VI 100/25 micrograms once daily compared with vilanterol.

5.3 Preclinical Safety Data

Pharmacological and toxicological effects seen with fluticasone furoate, umeclidinium or vilanterol in nonclinical studies were those typically associated with glucocorticoids, muscarinic receptor antagonists, or $beta_2$-adrenergic receptor agonists. Administration of combined fluticasone furoate, umeclidinium and vilanterol to dogs did not result in any significant new toxicity or any major exacerbation of expected findings associated with fluticasone furoate, umeclidinium or vilanterol alone.

Carcinogenesis/mutagenesis

Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at AUC exposures 1.4- or 2.9-fold, respectively, those in humans given fluticasone furoate 100 micrograms.

Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 20- or ≥ 17-fold the human clinical exposure at 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 rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 0.9- or 22-fold, respectively, the human clinical exposure of vilanterol at 25 micrograms based on AUC.

Reproductive Toxicology

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

Fluticasone furoate was not teratogenic in rats or rabbits, but delayed development in rats and caused abortion in rabbits at maternally toxic inhaled doses. There were no effects on development in rats at exposures 6.6-fold the human clinical exposure at 100 micrograms, based on AUC. Fluticasone furoate had no adverse effect on pre- or post-natal development 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 61-fold the human clinical exposure at 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). When given subcutaneously there were no effects at exposures 62-fold the human clinical exposure at 25 micrograms, based on AUC. Vilanterol had no adverse effect on pre- or post-natal development in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

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

Magnesium stearate

6.2 Incompatibilities

Not available.

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 1 month.

Write the date that 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

The storage conditions are indicated on the packaging.

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 beige 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.

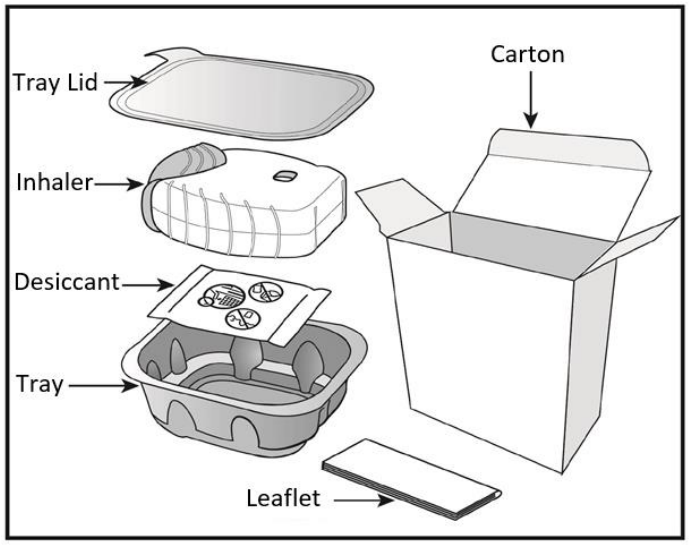
The inhaler contains two strips of 14 or 30 regularly distributed blisters, each containing

a white powder.

6.6 Instructions for Use/Handling

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

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 1 month from the date you first open the tray. See packaging for "Discard by" date. **After this date, the inhaler should no longer be used**.

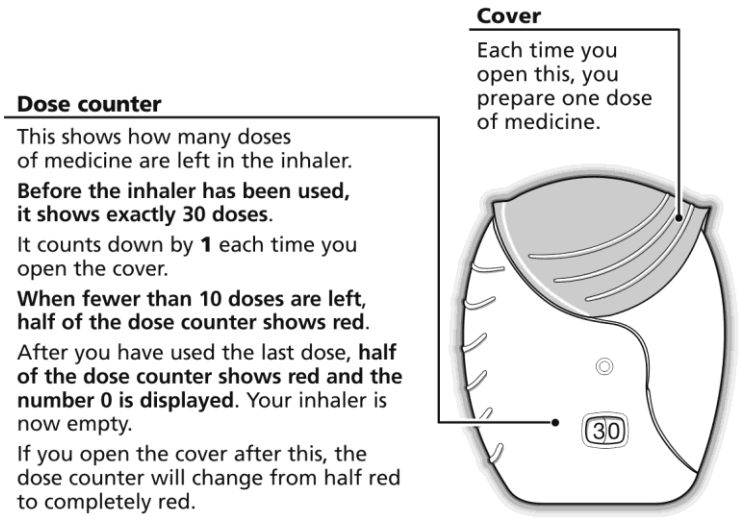
The step-by-step instructions shown below for the 30-dose (30 day supply) ***Ellipta*** inhaler

also apply to the 14-dose (14 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.

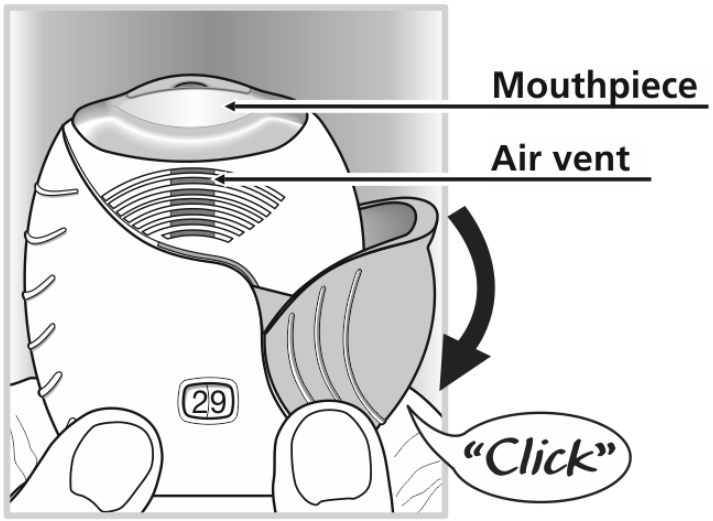


b) Prepare a dose

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.

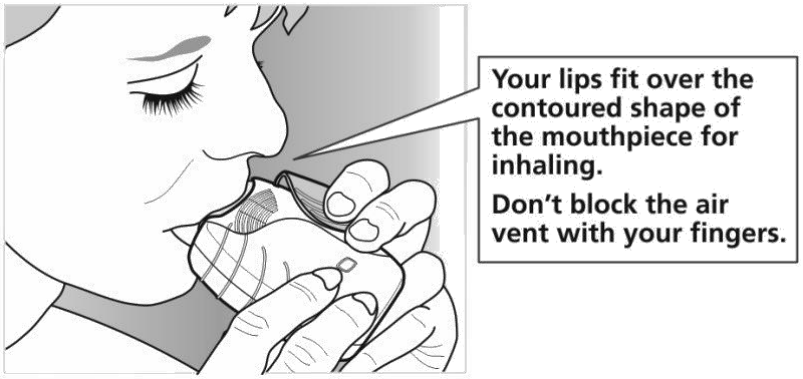
- **If the dose counter does not count down as you hear the "click", the inhaler will not deliver medicine. Take it back to your pharmacist for advice.**

- **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.**

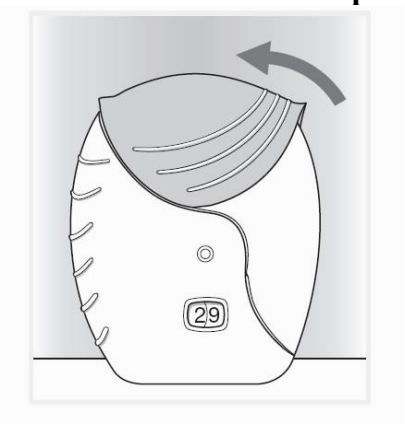
- **Breathe out slowly and gently.**

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 and rinse your mouth

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



- **Rinse your mouth with water after you have used the inhaler, do not swallow.**
  This will make it less likely that you will develop a sore mouth or throat as side effects.

Not all presentations are available in every country.

7. Marketing Authorization Holder

GlaxoSmithKline (Thailand) Ltd.

8. Marketing Authorization Number

2C 4/64 (NC)

9. Date of authorization

27 September 2021

10. Date of revision of the text

09 December 2022

Thai FDA mandatory warnings:

1. Do not use in patients with known hypersensitivity to this medicine.
2. Do not use in patients infected with disseminated fungal infection, except in case of necessity.
3. Use with caution in patients with stomach or intestinal ulcers, diabetes mellitus, tuberculosis, viral infections.

Version number: GDS12/IPI13

Date of issue: 09 December 2022

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Trelegy Ellipta IPI 13 TH