TRELEGY ELLIPTA

Fluticasone furoate/umeclidinium/vilanterol

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-dispensed dose contains either 100 micrograms fluticasone furoate, 62.5 micrograms umeclidinium (equivalent to 74.2 micrograms umeclidinium bromide) and 25 micrograms vilanterol (as trifenatate) or 200 micrograms fluticasone furoate, 62.5 micrograms umeclidinium (equivalent to 74.2 micrograms umeclidinium bromide) and 25 micrograms vilanterol (as trifenatate).

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece of the inhaler) containing 92 micrograms fluticasone furoate, 55 micrograms umeclidinium (equivalent to 65 micrograms umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate) or 184 micrograms fluticasone furoate, 55 micrograms umeclidinium (equivalent to 65 micrograms umeclidinium bromide) and 22 micrograms vilanterol (as trifenatate).

CLINICAL INFORMATION

Indications

ASTHMA

Trelegy Ellipta is indicated for the maintenance treatment of asthma in patients aged 18 years and older who are not adequately controlled with a combination of a long-acting beta2-agonist and an inhaled corticosteroid.

COPD

Trelegy Ellipta is indicated for maintenance treatment to prevent and relieve symptoms associated with moderate to severe chronic obstructive pulmonary disease (COPD) in patients who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (see *Clinical Studies*).

Dosage and Administration

Pharmaceutical form: Inhalation powder, pre-dispensed

Posology

Administer 1 actuation of Trelegy Ellipta once daily by oral inhalation.

After inhalation, rinse the mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

Trelegy Ellipta should be used at the same time every day. Do not use Trelegy Ellipta more than 1 time every 24 hours.

Populations

ASTHMA

Patients should be made aware that Trelegy Ellipta must be used regularly, even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Patients should be regularly reassessed by a healthcare professional so that the strength of Trelegy Ellipta they are receiving remains optimal and is only changed on medical advice.

Adults

The recommended starting dosage of Trelegy Ellipta for maintenance treatment of asthma is fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg (1 actuation of Trelegy Ellipta 100/62.5/25 mcg) or fluticasone furoate 200 mcg, umeclidinium 62.5 mcg, and vilanterol 25 mcg (1 actuation of Trelegy Ellipta 200/62.5/25 mcg) once daily, by oral inhalation.

When choosing the starting dosage strength of Trelegy Ellipta, consider the patients' disease severity; their previous asthma therapy, including the inhaled corticosteroid (ICS) dosage; as well as the patients' current control of asthma symptoms and risk of future exacerbation.

The maximum recommended dosage is 1 inhalation of Trelegy Ellipta 200/62.5/25 mcg once daily.

For patients who do not respond adequately to Trelegy Ellipta 100/62.5/25 mcg once daily, increasing the dose to Trelegy Ellipta 200/62.5/25 mcg once daily may provide additional improvement in asthma control. For patients who do not respond adequately to Trelegy Ellipta 200/62.5/25 mcg once daily, re-evaluate and consider other therapeutic regimens and additional therapeutic options.

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist (rescue medicine, e.g., albuterol) should be used for immediate relief.

Children and adolescents

The safety and efficacy of Trelegy Ellipta have not been established in children or adolescents less than 18 years of age.

COPD

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 to the COPD indication for this product.

ASTHMA and COPD

Elderly

No dosage adjustment is required in patients over 65 years (see *Pharmacokinetics*).

Renal impairment

No dosage adjustment is required for patients with renal impairment (see *Pharmacokinetics*).

Hepatic impairment

Caution should be exercised when dosing patients with hepatic impairment who may be more at risk of systemic adverse reactions associated with corticosteroids. For patients with moderate or severe hepatic impairment the maximum dose is 100/62.5/25 micrograms (see *Warnings and Precautions, Pharmacokinetics*).

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.

Warnings and Precautions

<u>Exacerbations</u>

Trelegy Ellipta should not be used to treat acute asthma symptoms or an acute exacerbation in COPD for which a short-acting bronchodilator is required.

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, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with Trelegy Ellipta. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of Trelegy Ellipta.

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

For patients with moderate to severe hepatic impairment receiving Trelegy Ellipta, the 100/62.5/25 micrograms dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions (see *Dosage and Administration*, *Pharmacokinetics*).

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, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression.

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 *Adverse Reactions*). 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.

An increased incidence of pneumonia in patients with asthma receiving higher doses of Trelegy Ellipta cannot be excluded. This is based on clinical experience with fluticasone furoate/vilanterol, where there was a trend toward an increased risk of pneumonia for fluticasone furoate/vilanterol 200/25 micrograms compared with fluticasone furoate/vilanterol 100/25 micrograms and placebo.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Hyperglycaemia

There have been reports of increases in blood glucose levels with fluticasone furoate/vilanterol. This should be considered in patients with a history of, or with risk factors for, diabetes mellitus.

Interactions

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 *Pharmacokinetics*).

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 *Adverse Reactions, Overdose*).

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 *Non-Clinical Information*).

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 *Non-Clinical Information*).

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

Lactation

It is unknown whether 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.

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.

Adverse Reactions

Clinical trial data

Data from one asthma phase III clinical study and three COPD phase III clinical studies were used to determine the frequency of adverse reactions associated with Trelegy Ellipta (see *Table 1*). In the asthma clinical development program, a total of 1,623 adult subjects were assessed for adverse reactions. In the COPD clinical development program, a total of 5,589 adult subjects were included in an integrated assessment of adverse reactions.

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

Adverse reactions are listed by MedDRA system organ class and by frequency (see *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: ≥1/1000 to <1/100
Rare: ≥1/10000 to <1/1000
Very rare: <1/10000

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 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 *Warnings and Precautions*)

COPD

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.

Asthma

In patients with asthma (study 205715) treated up to 52 weeks, the incidence of pneumonia was 1% (5 of 406 patients) for Trelegy Ellipta 100/62.5/25 micrograms and <1% (4 of 408 patients) for Trelegy Ellipta 200/62.5/25 micrograms. The incidence of pneumonia was 2% in the fluticasone furoate/vilanterol 100/25 micrograms (7 of 407 patients) and fluticasone furoate/vilanterol 200/25 micrograms (7 of 406 patients) groups. The incidence of pneumonia events requiring hospitalisation was similar in the Trelegy Ellipta and fluticasone furoate/vilanterol groups (<1% for all groups). There were no fatal pneumonia events.

Post-marketing data

System organ class	Adverse reaction(s)	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	Uncommon
	Intraocular pressure increased	Rare
Cardiac disorders	Palpitations	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Rare
Renal and urinary disorders	Urinary retention, dysuria	Rare

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 *Warnings and Precautions, Pharmacodynamics*).

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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 asthma and 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 1,504 subjects with asthma exposed to Trelegy Ellipta for up to 24 weeks, or in a subset of 360 subjects exposed for up to 52 weeks.

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.

Pharmacokinetics

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 (FF/VI) combination, umeclidinium/vilanterol (UMEC/VI) combination, or each component as monotherapy.

Population pharmacokinetic (PK) analyses were conducted to assess the systemic exposure of fluticasone furoate, umeclidinium, and vilanterol in subjects with asthma. In these analyses, systemic drug levels (steady-state C_{max} and AUC_{0-24}) of fluticasone furoate and vilanterol following fluticasone furoate/umeclidinium/vilanterol (100/62.5/25 micrograms and 200/62.5/25 micrograms) in one inhaler (triple combination) were within the range of those observed following administration of the dual combination of FF/VI with the respective 100 micrograms and 200 micrograms FF doses; the systemic exposure of umeclidinium 62.5 micrograms following fluticasone furoate/umeclidinium/vilanterol in one inhaler was within the range of those observed following administration of umeclidinium 62.5 micrograms as monotherapy.

Population PK analyses for fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 micrograms were conducted using a combined PK dataset from three phase III studies in 821 COPD subjects. In these analyses, systemic drug levels (steady-state C_{max} and AUC_{0-24}) 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 administered 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 P-gp 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 the asthma population pharmacokinetic analyses (1,265 subjects for fluticasone furoate; 1,263 subjects for vilanterol; 634 subjects for umeclidinium), the impact of demographic covariates (race/ethnicity, age, gender, weight) on the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol was evaluated. In a COPD 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

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

In East Asian subjects with asthma (Japanese, East Asian and Southeast Asian heritage) (n = 92) who provided fluticasone furoate/umeclidinium/vilanterol (100/62.5/25 micrograms and 200/62.5/25 micrograms) population pharmacokinetic data, estimates of vilanterol C_{max} at steady state was approximately 3-fold higher than non-East Asian subjects. There was no effect of race on pharmacokinetics of fluticasone furoate or umeclidinium in subjects with asthma.

In East Asian subjects with COPD (Japanese and East Asian Heritage) (n = 113) who received fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 micrograms, 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.

Elderly

No clinically relevant effects requiring dose adjustment based on age were observed for subjects with asthma or COPD.

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 < 30mL/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. No clinically relevant effects on weighted mean serum cortisol were observed in subjects with mild hepatic impairment (Child-Pugh A). 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). For patients with moderate or severe hepatic impairment, the maximum dose is 100/62.5/25 micrograms (see *Dosage and Administration*).

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). *In vitro* protein binding studies between subjects with moderate hepatic impairment and healthy volunteers were conducted, and no clinically significant evidence of altered protein binding was seen.

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 for subjects with asthma or COPD.

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

Clinical Studies

Asthma

The safety and efficacy of Trelegy Ellipta (FF/UMEC/VI) were evaluated in 2,436 subjects in a randomised, multi-centre, active-controlled, double-blind clinical trial of 24 to 52 weeks' duration in adult subjects with asthma inadequately controlled on their current treatments of combination therapy (ICS plus a LABA) (study 205715, CAPTAIN). The trial evaluated the efficacy of Trelegy Ellipta on lung function, annualized rate of moderate and severe asthma exacerbations, asthma symptom control, and health-related quality of life when compared with fluticasone furoate/vilanterol. The primary endpoint was change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 24. The key secondary endpoint was the annualized rate of moderate/severe asthma exacerbation.

This trial had a 5-week run-in/stabilization period described as follows: subjects inadequately controlled [Asthma Control Questionnaire (ACQ-6) ≥1.5] on their current asthma treatment of inhaled corticosteroid (greater than or equivalent to fluticasone propionate 250 micrograms per day) plus LABA entered a 3-week run-in period of treatment with fluticasone proprionate/salmeterol 250/50 micrograms twice daily. Subjects who remained inadequately controlled (ACQ-6 ≥1.5) after the run-in period were transferred to fluticasone furoate/vilanterol (FF/VI) 100/25 micrograms once daily

for a 2-week stabilization period. Across all treatment groups, baseline demographics were similar.

At screening, the mean prebronchodilator percent predicted FEV_1 was 58.5% (SD: 12.8%); the mean percent reversibility was 29.9% (SD: 18.1%), with a mean absolute reversibility of 0.484 L (SD: 0.274 L), and the mean ACQ-6 score was 2.5 (SD: 0.6). During the 5-week run in/stabilization period, subjects had substantial improvements in both lung function (trough FEV_1 improvement of 0.287 L) and asthma control (mean ACQ-6 score decreased by 0.6). Despite these improvements, a majority of subjects (93%) were not well controlled (mean score ACQ-6 of 1.9), demonstrating the need for additional therapy. At randomization, the mean prebronchodilator percent predicted FEV1 was 68.2% (SD: 14.8%).

After the 5-week run-in/stabilization period, eligible subjects were randomised to receive once-daily inhalations of Trelegy Ellipta 100/62.5/25 micrograms (n = 406), Trelegy Ellipta 200/62.5/25 micrograms (n = 408), FF/UMEC/VI 100/31.25/25 micrograms (n = 405), FF/UMEC/VI 200/31.25/25 micrograms (n = 404), FF/VI 100/25 micrograms (n = 407), or FF/VI 200/25 micrograms (n = 406).

While 4 doses of Trelegy Ellipta were studied in the trial, efficacy data results shown are for Trelegy Ellipta 100/62.5/25 micrograms and Trelegy Ellipta 200/62.5/25 micrograms, the recommended doses for the treatment of asthma. In the evaluation of efficacy, the non-lung function endpoint analyses included prespecified pooled comparisons of Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) with FF/VI (100/25 and 200/25 micrograms).

The change from baseline in trough FEV_1 at Week 24 (primary efficacy endpoint) showed statistically significant improvements in lung function for both Trelegy Ellipta 100/62.5/25 micrograms and Trelegy Ellipta 200/62.5/25 micrograms compared with FF/VI 100/25 micrograms and for Trelegy Ellipta 200/62.5/25 micrograms compared with FF/VI 200/25 micrograms and FF/VI 200/25 micrograms, respectively. (see *Table 2, Figures 1 and 2*).

Table 2. Lung function endpoints (Study 205715)

	FF/VI 100/25 (n = 407)	Trelegy Ellipta FF/UMEC/VI 100/62.5/25 (n = 406)	FF/VI 200/25 (n = 406)	Trelegy Ellipta FF/UMEC/VI 200/62.5/25 (n = 408)
Trough FEV$_1$ (L) at Week 24				
LS mean change from baseline (SE)	0.024 (0.0157)	0.134 (0.0155)	0.076 (0.0156)	0.168 (0.0155)
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI p-value	Reference	0.110 0.066, 0.153 p<0.001	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI p-value	---	---	Reference	0.092 0.049, 0.135 p<0.001
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25[a] Treatment difference 95% CI	---	Reference	---	0.034 -0.009, 0.077
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25[a] Treatment difference 95% CI	---	0.059 0.015, 0.102	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25[a] Treatment difference 95% CI	Reference	---	---	0.143 0.100, 0.187
FEV$_1$ at 3 hours post-dose[b] (L) at Week 24				
LS mean change from baseline (SE)	0.132 (0.0160)	0.243 (0.0158)	0.168 (0.0159)	0.286 (0.0158)
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI	Reference	0.111 0.067, 0.155	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI	---	---	Reference	0.118 0.074, 0.162
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Treatment difference 95% CI	---	Reference	---	0.044 0, 0.087
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI	---	0.075 0.031, 0.119	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI	Reference	---	---	0.155 0.110, 0.199

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

[a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity.

[b] Endpoint was not in the predefined testing hierarchy, therefore not adjusted for multiplicity.

Figure 1. Least Squares (LS) Mean Change from Baseline in Trough FEV$_1$ (L) for Trelegy Ellipta 100/62.5/25 micrograms

*p<0.001 FF/UMEC/VI 100/62.5/25 versus FF/VI 100/25
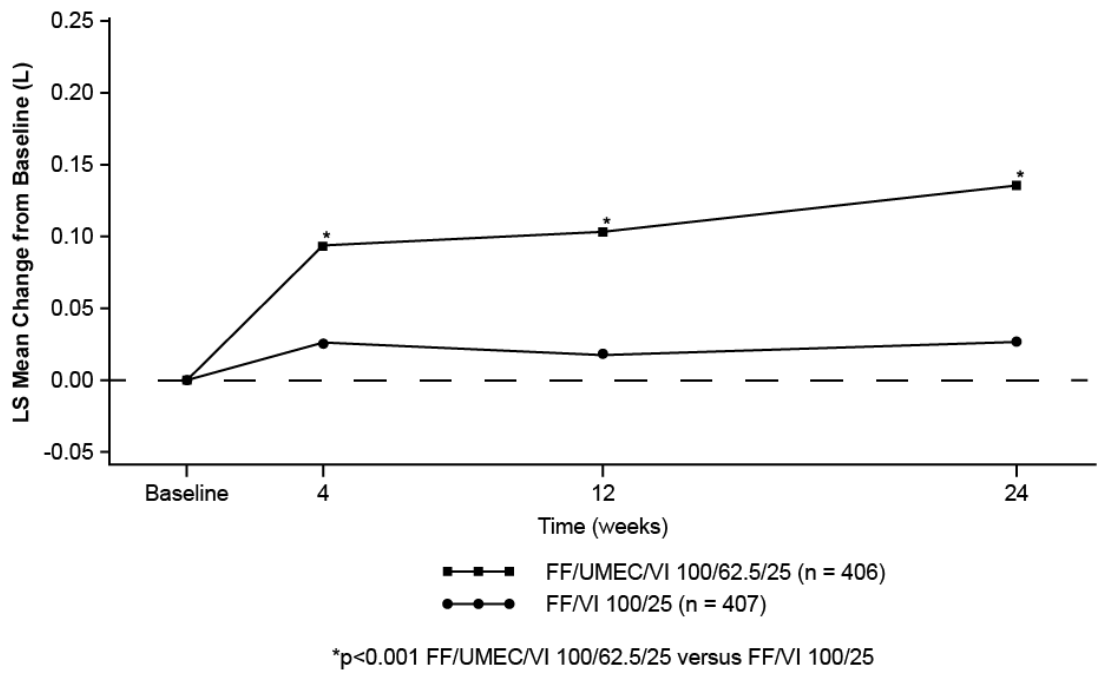
Figure 2. Least Squares (LS) Mean Change from Baseline in Trough FEV$_1$ (L) for Trelegy Ellipta 200/62.5/25 micrograms

*p<0.001 FF/UMEC/VI 200/62.5/25 versus FF/VI 200/25
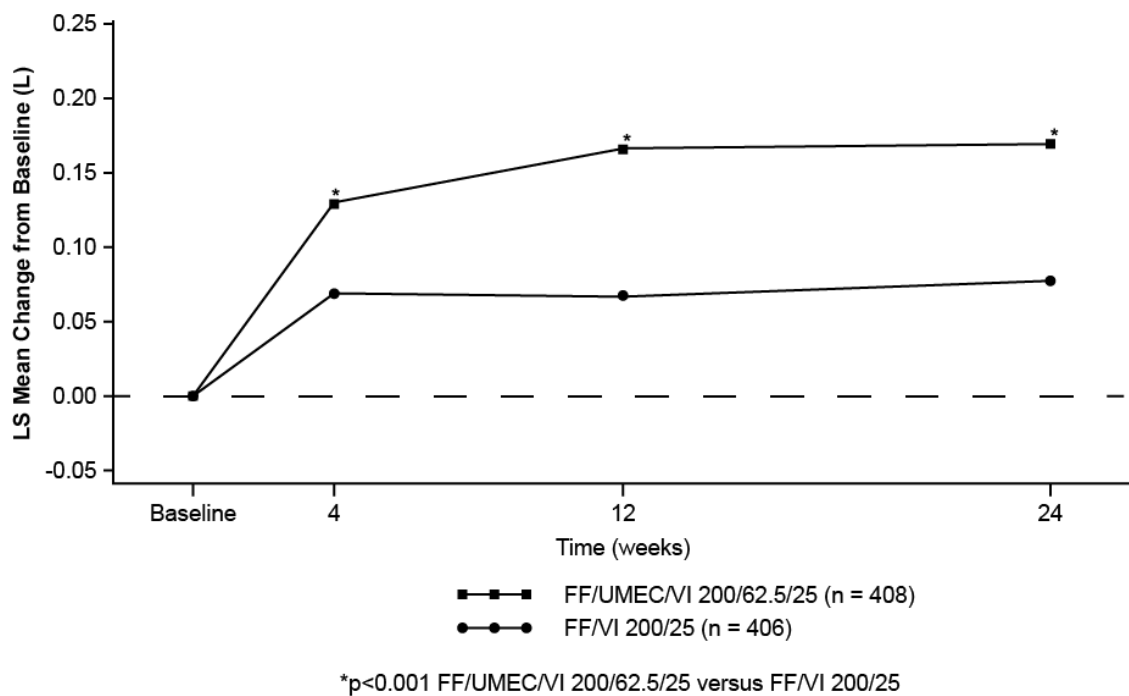
Moderate/severe asthma exacerbations were assessed over the 52-week treatment period (see *Table 3*). In the pooled analysis, the annualized rate of moderate/severe

exacerbations was numerically lower with Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) compared with FF/VI (100/25 and 200/25 micrograms) (13% reduction in rate; 95% CI: -5.2, 28.1). Descriptive analyses of unpooled treatment comparisons for the annualized rate of moderate/severe exacerbations are also provided.

Table 3. Annualised Rate of Moderate/severe Exacerbations[a] (Up to 52 Weeks) (Study 205715)

	FF/VI 100/25 (n = 407)	Trelegy Ellipta FF/UMEC/VI 100/62.5/25 (n = 406)	FF/VI 200/25 (n = 406)	Trelegy Ellipta FF/UMEC/VI 200/62.5/25 (n = 408)
Mean Annualised Rate	0.87	0.68	0.57	0.55
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Reduction in Rate (%) 95% CI	Reference	21.8% -1.1, 39.5	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Reduction in Rate (%) 95% CI	---	---	Reference	3.2% -28.2, 27.0
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Reduction in Rate (%) 95% CI	---	Reference	---	19.1% -6.4, 38.5
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Change in Rate (%) 95% CI	---	-19.6%[b] -57.2, 9.0	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Reduction in Rate (%) 95% CI	Reference	---	---	36.7% 17.6, 51.5
CI=confidence interval; n=number in the intent-to-treat population. [a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity. [b] Negative percentage reflects an increase in exacerbation rate for FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25.				

In addition, severe asthma exacerbations were assessed. In a descriptive pooled analysis, a difference in the mean annualised rate of severe exacerbations was not observed for Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) compared with FF/VI (100/25 and 200/25 micrograms) (2.6% reduction in rate; 95% CI: -26.2, 24.9). The mean annualised rates of severe exacerbations were 0.41 and 0.23 for Trelegy Ellipta 100/62.5/25 micrograms and Trelegy Ellipta 200/62.5/25 micrograms, respectively. The mean annualised rates of severe exacerbations were 0.38 and 0.26 for FF/VI 100/25 micrograms and FF/VI 200/25 micrograms, respectively.

Patient symptoms and health-related quality of life were assessed using the ACQ, the Evaluating Respiratory Symptoms in Asthma (E-RS:Asthma), and the St. George's Respiratory Questionnaire (SGRQ) (see *Table 4*). In a descriptive pooled analysis, the ACQ-7 responder rate was 63% for Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) compared with 55% for FF/VI (100/25 and 200/25 micrograms) at Week 24

(OR: 1.43; 95% CI: 1.16, 1.76). Descriptive analyses of unpooled treatment comparisons are also provided.

Table 4. Asthma Control Questionnaire (ACQ)-7 Results[a] at Week 24 (Study 205715)

	FF/VI 100/25 (n = 407)	Trelegy Ellipta FF/UMEC/VI 100/62.5/25 (n = 406)	FF/VI 200/25 (n = 406)	Trelegy Ellipta FF/UMEC/VI 200/62.5/25 (n = 408)
Responder[b] (%)	52%	62%	58%	64%
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Odds Ratio 95% CI	Reference	1.59 1.18, 2.13	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Odds Ratio 95% CI	---	---	Reference	1.28 0.95, 1.72
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Odds Ratio 95% CI	---	Reference	---	1.08 0.80, 1.45
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Odds Ratio 95% CI	---	1.19 0.88, 1.60	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Odds Ratio 95% CI	Reference	---	---	1.71 1.27, 2.30
CI=confidence interval; n=number in the intent-to-treat population [a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity. [b] Defined as an ACQ-7 score ≥0.5 below baseline.				

The ACQ-5 (comprising the 5 questions on symptoms from ACQ-7) responder rates at Week 24 were similar to the ACQ-7 results. In a pooled descriptive analysis, the ACQ-5 responder rate was 64% for Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) compared with 60% for FF/VI (100/25 and 200/25 micrograms) (OR: 1.23; 95% CI: 1.00, 1.52) at Week 24.

In an unpooled descriptive analysis, the ACQ-5 responder rate was 63% for Trelegy Ellipta 100/62.5/25 micrograms compared with 58% for FF/VI 100/25 micrograms (OR: 1.28; 95% CI: 0.96, 1.72) at Week 24. The ACQ-5 responder rate was 66% for Trelegy Ellipta 200/62.5/25 micrograms compared with 62% for FF/VI 200/25 micrograms (OR: 1.19; 95% CI: 0.88, 1.60) at Week 24.

In a pooled descriptive analysis, the E-RS:Asthma responder rate (defined as a decrease in score of ≥2 from baseline) was 45% with Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) compared with 41% for FF/VI (100/25 and 200/25 micrograms) (OR: 1.18; 95% CI: 0.96, 1.45) (Weeks 21-24).

In an unpooled descriptive analysis, the E-RS:Asthma responder rate was 42% for Trelegy Ellipta 100/62.5/25 micrograms compared with 38% for FF/VI 100/25 micrograms (OR: 1.22; 95% CI: 0.91, 1.63) (Weeks 21-24). The E-RS:Asthma responder rate was 47% for Trelegy Ellipta 200/62.5/25 micrograms compared with 44% for FF/VI 200/25 micrograms (OR: 1.15; 95% CI: 0.86, 1.53) (Weeks 21-24).

In a pooled descriptive analysis, the SGRQ responder rate (defined as a decrease in score of ≥4 from baseline) was 69% for Trelegy Ellipta (100/62.5/25 and 200/62.5/25 micrograms) compared with 66% for FF/VI (100/25 and 200/25 micrograms) (OR: 1.14; 95% CI: 0.92, 1.42) at Week 24.

In an unpooled descriptive analysis, the SGRQ responder rate was 68% for Trelegy Ellipta 100/62.5/25 micrograms compared with 64% for FF/VI 100/25 micrograms (OR: 1.26; 95% CI: 0.93, 1.70) at Week 24. The SGRQ responder rate was 69% for Trelegy Ellipta 200/62.5/25 micrograms compared with 68% for FF/VI 200/25 micrograms (OR: 1.04; 95% CI: 0.76, 1.41) at Week 24.

COPD

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).

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 5*). 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 5*).

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 5*).

Table 5. 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).
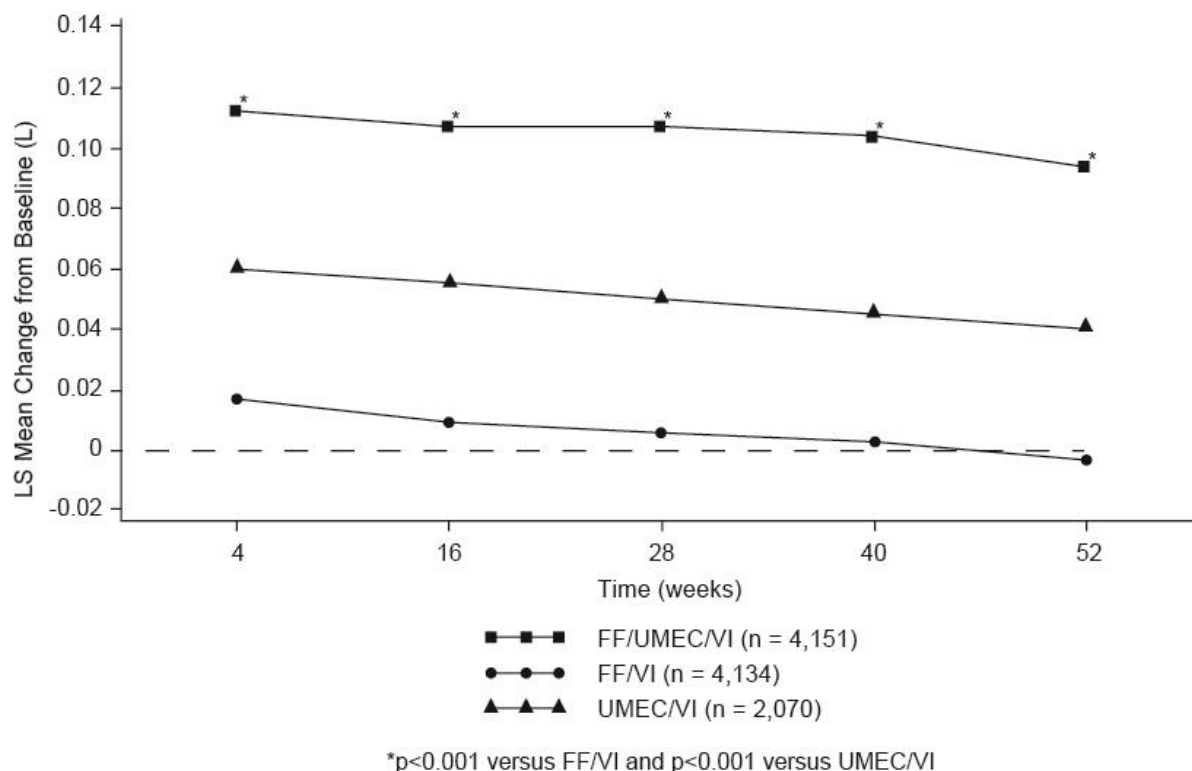
Patients treated with Trelegy Ellipta demonstrated a statistically significant reduction in the annual rate of on-treatment moderate/severe exacerbations (primary endpoint) compared with FF/VI and compared with UMEC/VI. See *Table 6* for efficacy endpoint results.

Table 6. 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 3*).

Figure 3. Least Squares (LS) Mean Change from Baseline in Trough FEV1 (L)

*p<0.001 versus FF/VI and p<0.001 versus UMEC/VI

Treatment with Trelegy Ellipta significantly reduced the risk of all-cause mortality including on- and off-treatment data, by 27.7% compared with UMEC/VI (vital status confirmed in 99.6% of patients at Week 52) (see *Table 7*). The risk reduction of all-cause mortality was 11.3% with Trelegy Ellipta compared with FF/VI; however, this result was not statistically significant.

Table 7. Reduction in All-Cause Mortality (Study CTT116855)

Treatment	n	Hazard Ratio vs. Comparator (95% CI)	Reduction in Risk (95% CI)	p-value
Trelegy Ellipta FF/UMEC/VI	4,151			
UMEC/VI	2,070	0.72 (0.53, 0.99)	27.7% (1.2, 47.1)	0.042
FF/VI	4,134	0.89 (0.67, 1.16)	11.3% (-16.5, 32.5)	0.387
CI=confidence interval.				

Analysis of on-treatment all-cause mortality were also conducted, and results were consistent with the above results. Treatment with Trelegy Ellipta significantly reduced the risk of on-treatment all-cause mortality by 42.1% (95% CI: 11.9, 61.9; p=0.011) compared with UMEC/VI. The reduction in risk of all-cause mortality was 5.5% (95%

CI: -40.2, 36.3) with Trelegy Ellipta compared with FF/VI; however, this result was not statistically significant.

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 8*) 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 8*) 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 8. 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, Trelegy Ellipta 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.

Umeclidinium with fluticasone furoate/vilanterol

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 FEV_1 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.

Non-Clinical Information

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 0.6 or 1.3-fold, respectively, those in humans given fluticasone furoate 200 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 3.0-fold the human clinical exposure at 200 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.

PHARMACEUTICAL INFORMATION

List of Excipients

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

Magnesium stearate

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.

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.

In-use storage condition

The in-use storage condition is indicated on the packaging.

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.
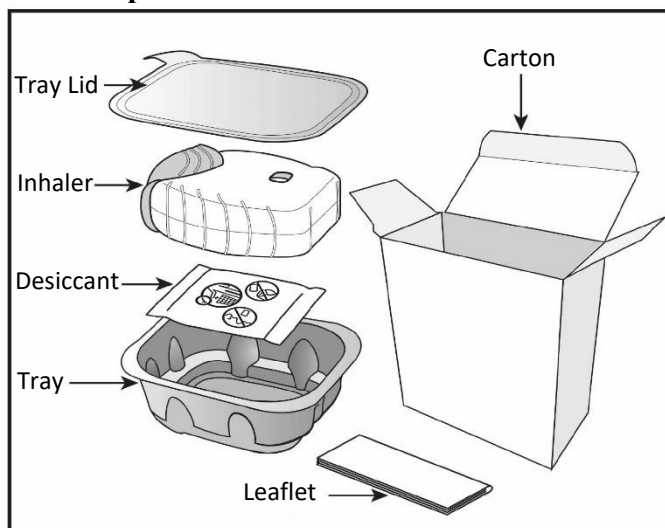
Not all presentations are available locally.

Incompatibilities

None

Use and 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**.

If you forget to use Trelegy Ellipta, don't take an extra dose to make up for a missed dose. Just take your next dose at the usual time.

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.

Cover
Each time you open this, you prepare one dose of medicine.

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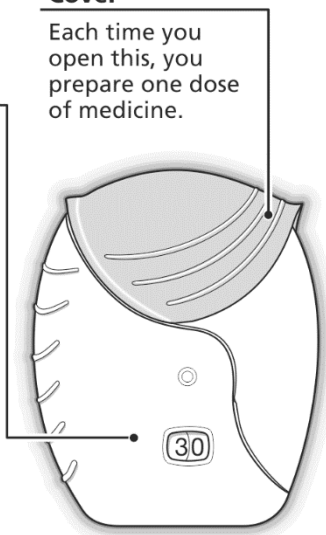It counts down by **1** each time you open the cover.
When fewer than 10 doses are left, half of the dose counter shows red.
After you have used the last dose, **half of the dose counter shows red and the number 0 is displayed**. Your inhaler is now empty.
If you open the cover after this, the dose counter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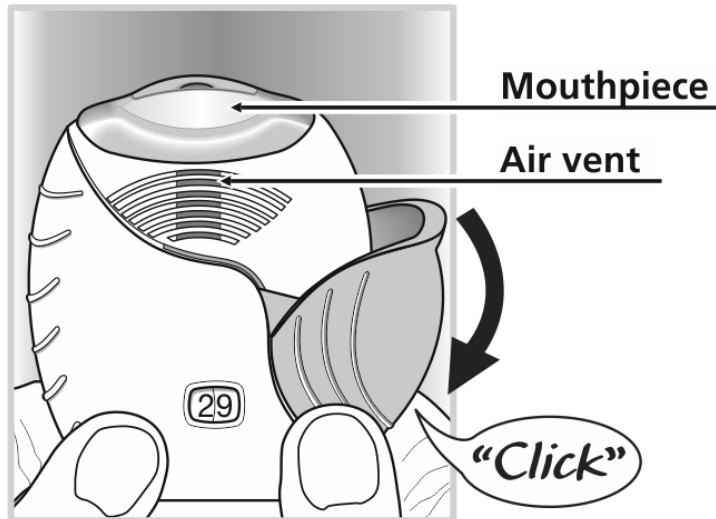
b) **Prepare a dose**

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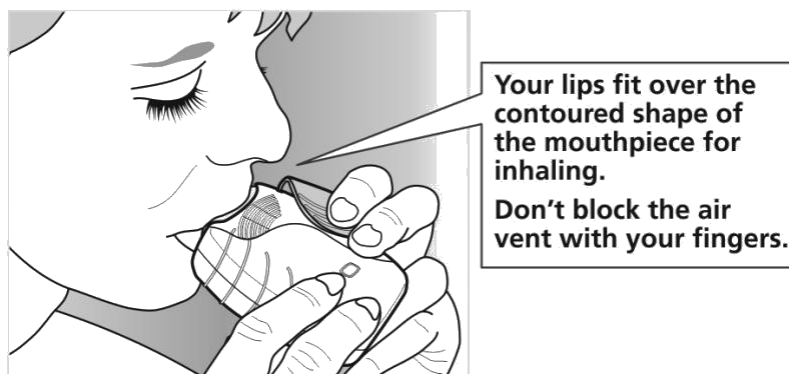
- **Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).**
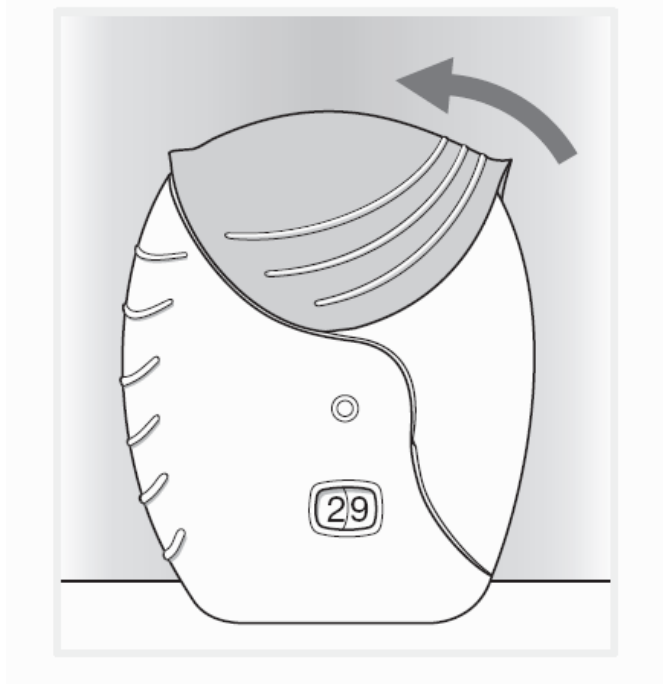
- **Remove the inhaler from your mouth.**

- **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.

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