For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

TRELEGY ELLIPTA

1. GENERIC NAME

Fluticasone Furoate, Umeclidinium and Vilanterol Powder for Inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-dispensed dose contains 100 micrograms of fluticasone furoate Ph. Eur. 62.5 micrograms umeclidinium (equivalent to 74.2 micrograms umeclidinium bromide) and 25 micrograms of vilanterol (as trifenatate).

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

List of Excipients

Lactose monohydrate (which contains milk protein) (see *4.3 Contraindications*) (25 milligram lactose monohydrate per blister), Magnesium stearate.

3. DOSAGE FORM AND STRENGTH

Powder for Inhalation, pre-dispensed.

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

Ellipta:

TRELEGY ELLIPTA is a plastic inhaler containing two foil blister strips. Each foil strip contains 14 or 30 regularly distributed blisters with one strip containing 100 micrograms of fluticasone furoate and the other strip containing 62.5 micrograms of umeclidinium and 25 micrograms of vilanterol.

Fluticasone furoate/umeclidinium/vilanterol is available in two pack sizes, delivering either 14 or 30 inhalations per Ellipta inhaler.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

TRELEGY ELLIPTA is indicated for maintenance treatment to prevent and relieve symptoms associated with chronic obstructive pulmonary disease (COPD).

4.2 Posology and Method of Administration

TRELEGY ELLIPTA is for oral inhalation only. *TRELEGY ELLIPTA* should be administered once daily, either morning or evening, but at the same time each day.

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

Populations

Adults

The recommended and maximum dose is one inhalation of *TRELEGY ELLIPTA* 100/62.5/25 micrograms once daily.

Children and adolescents

Use in patients less than 18 years of age is not relevant to the COPD indication for this product.

Elderly

No dosage adjustment is required in patients over 65 years (see *5.3 Pharmacokinetic Properties*).

Renal impairment

No dose adjustment is required for patients with renal impairment (see *5.3 Pharmacokinetic Properties*).

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 *4.4 Special Warnings and Precautions for Use* and *5.3 Pharmacokinetics Properties*).

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 Precautions for Use

Exacerbations

TRELEGY ELLIPTA should not be used to treat 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* 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

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 *4.2 Posology and Method of Administration* and *5.3 Pharmacokinetic Properties*).

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 *4.8 Undesirable Effects*). 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 Drug 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 *5.3 Pharmacokinetic properties*).

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 *4.8 Undesirable Effects and 4.9 Overdose*).

4.6 Use in Special Populations

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 *6 Non clinical Properties).*

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 *6 Non clinical Properties*).

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.

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

Data from three COPD phase III clinical studies were used to determine the frequency of adverse reactions associated with *TRELEGY ELLIPTA* (see *Table 1*). In the COPD clinical development program, a total of 5,589 adult subjects were included in an integrated assessment of adverse reactions.

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	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 *4.8 Special Warnings and 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 reaction(s)**	**Frequency**
Immune system disorders	Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and rash	Rare
Eye disorders	Vision blurred, glaucoma, eye pain	Uncommon
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 *4.4 Special Warnings and Precautions for Use* and *5.2 Pharmacodynamics 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

ATC code

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

5.1 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.

5.2 Pharmacodynamic Properties

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.

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

Population pharmacokinetic (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 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 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 COPD based on race were observed in fluticasone furoate, umeclidinium or vilanterol systemic exposure.

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 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 *4.2 Posology and Method of 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 COPD.

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

5.4 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).

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	0.0 (0.38)	-0.1 (0.39)	0.1	-

	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**
perform more activities than usual) over Weeks 1-24, LS mean change from baseline (SE)			(-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)

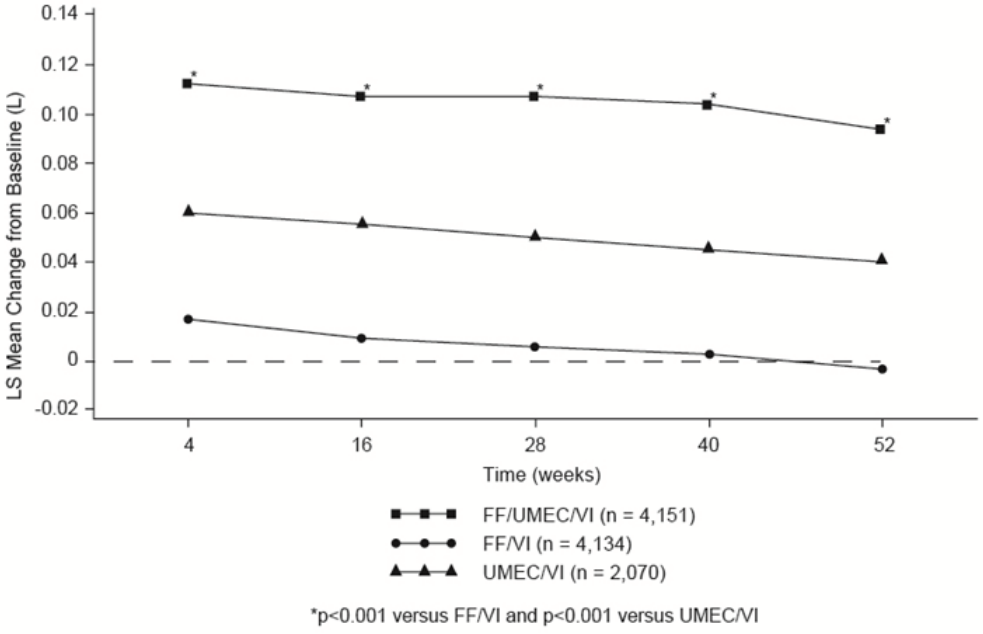
	***TRELEGY ELLIPTA* FF/UMEC/VI (n=4,151)**	**FF/VI (n = 4,134)**	**UMEC/VI (n = 2,070)**	***TRELEGY ELLIPTA* FF/UMEC/VI vs. FF/VI**	***TRELEGY ELLIPTA* FF/UMEC/VI vs. UMEC/VI**
Rate of Moderate/severe exacerbations [a]					
Exacerbations per year	0.91	1.07	1.21		
Reduction in Rate (%) 95% CI p-value				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				-1.8 -2.4, -1.1	-1.8 -2.6, -1.0

	***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**
p-value				p<0.001	p<0.001
Responders according to SGRQ Total Score at Week 52					
Responder [b] (%)	42%	34%	34%		
Odds Ratio 95% Cl 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)



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 4*). 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 4. 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.				

Analyses 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/days 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 5*) 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 5*) 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 5. 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/days 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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology and Pharmacology

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.

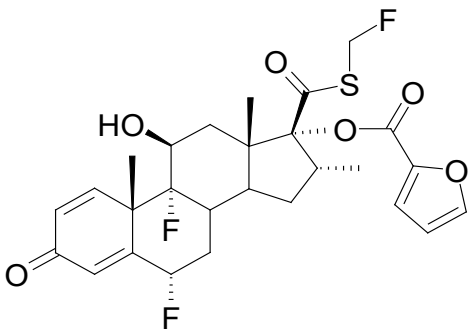
Umeclidinium was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium to rats resulted in lower maternal body weight gain and food consumption and slightly decreased pre-weaning pup body weights in dams given 180 micrograms/kg/day dose (approximately 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.

7. DESCRIPTION

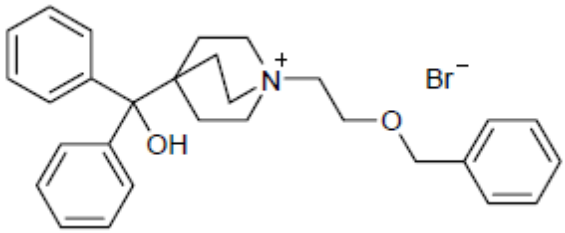
Chemical structure of fluticasone furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid. It has the chemical name (6α, 11β, 16α, 17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16 methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate, the molecular formula $C_{27}H_{29}F_3O_6S$ and the following chemical structure:



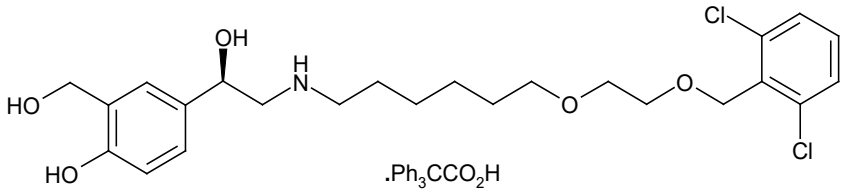
Chemical structure of umeclidinium bromide

Umeclidinium bromide is a muscarinic receptor antagonist. It has the chemical name 1- [2- (Benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide, the molecular formula $C_{29}H_{34}BrNO_2$ and the following chemical structure:



Chemical structure of vilanterol trifenatate

Vilanterol trifenatate is beta$_2$-adrenergic agonist. It has the chemical name Triphenylacetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1 hydroxyethyl}-2-(hydroxymethyl)phenol (1:1), the molecular formula $C_{24}H_{33}Cl_2NO_5$. $C_{20}H_{16}O_2$ and the following chemical structure:



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

No relevant data available

8.2 Shelf Life

24 months

The expiry date is indicated on the label and packaging.

In-use shelf-life

Following removal from the tray, the product may be stored for 1 month. The in-use shelf-life is indicated on the packaging.

8.3 Packaging Information

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.

8.4 Storage and Handling Information

Do not store above 30°C.

If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

Use and Handling

Keep out of sight and reach of children.

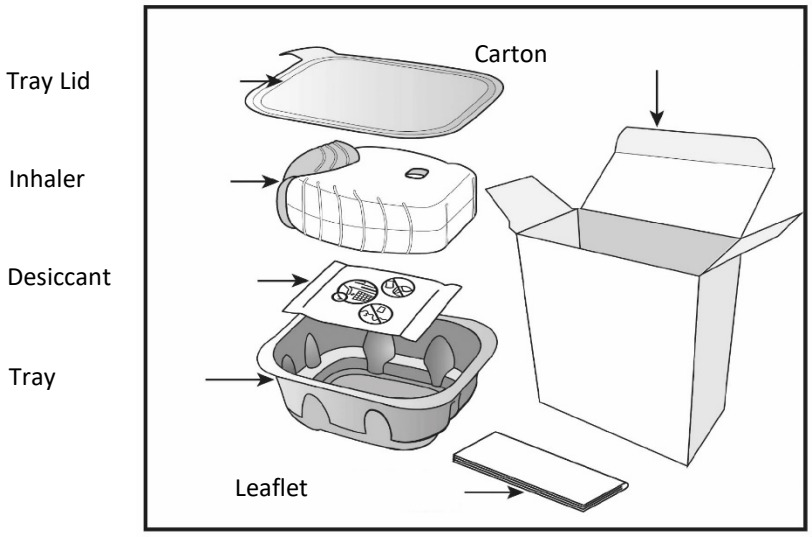
In-use storage condition

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

Keep the inhaler inside the sealed tray to protect from moisture and only remove immediately before first use.

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

Your Ellipta inhaler carton contains



The inhaler is packaged in a tray. **Do not open the tray until you are ready to inhale a dose of your medicine.** When you are ready to use your inhaler, peel back the lid to open the tray. The tray contains a desiccant sachet, to reduce moisture. Throw this desiccant sachet away — **don't** open, eat or inhale it.

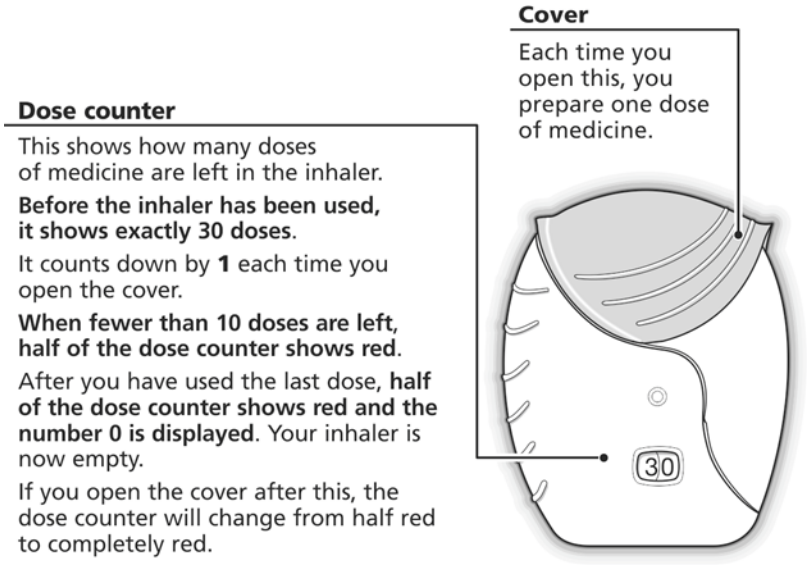
When you take the inhaler out of the sealed tray, it will be in the 'closed' position. **Don't open the inhaler until you are ready to inhale a dose of medicine.** Write the "Discard by" date on the inhaler label in the space provided.

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

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

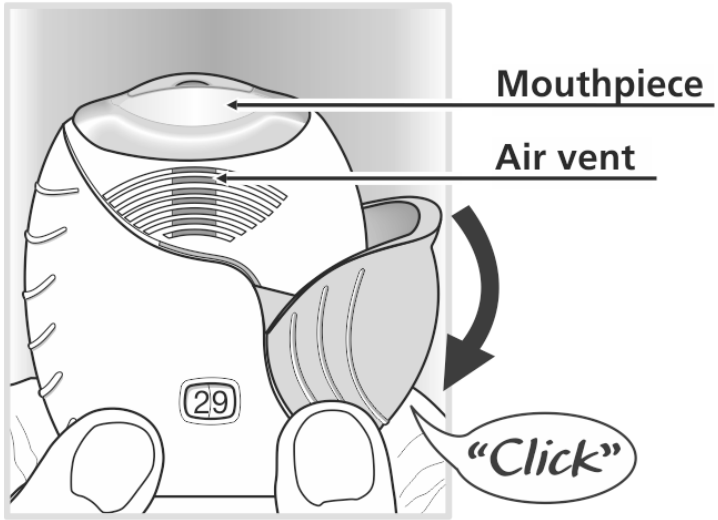


b) Prepare a dose

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.**

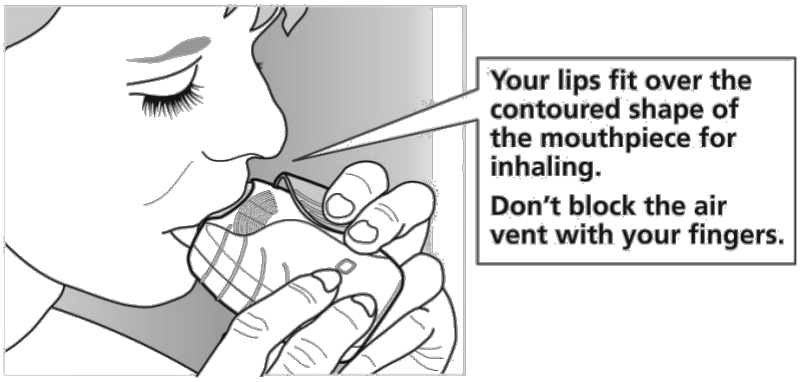
- **Do not shake the inhaler at any time.**

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.



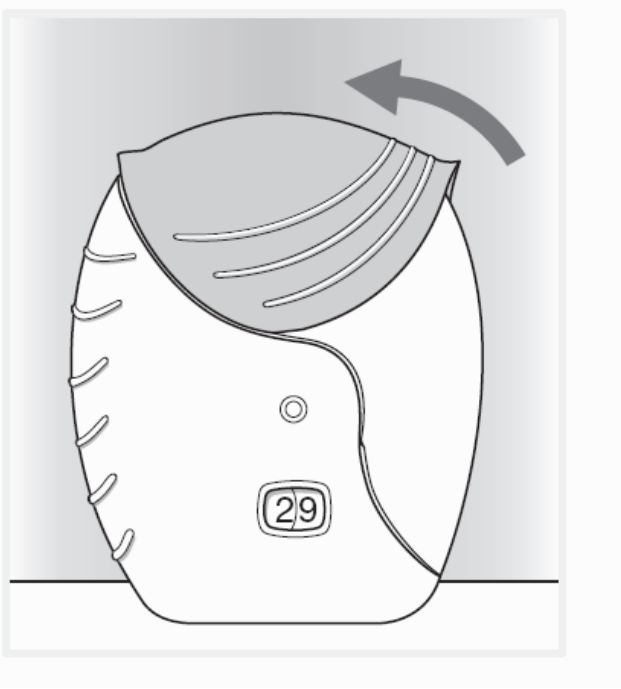
- **Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).**
- **Remove the inhaler from your mouth.**
- **Breathe out slowly and gently.**

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.

9. PATIENT COUNSELLING INFORMATION

Registered Medical Practitioners may counsel their patients (and/or their patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *TRELEGY ELLIPTA*. Patients (and/or their patient's caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

Manufactured by:
M/s. Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)
Priory Street, Ware,
Hertfordshire SG12 0DJ
United Kingdom.

For further information please contact:
M/s. GlaxoSmithKline Pharmaceuticals Limited
Registered Office: Dr. Annie Besant Road,
Worli, Mumbai 400 030, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Marketing Authorization Holder: M/s. GlaxoSmithKline Pharmaceuticals Limited, Dr. Annie Besant Road, Worli, Mumbai 400 030, India.

Marketing Authorization Details: IMP-80/2020 dated 18th May 2020

12. DATE OF REVISION

01-NOV-2023

Trademarks are owned by or licensed to the GSK group of companies.

TRELEGY ELLIPTA was developed in collaboration with Innoviva, Inc.

Version: TLG/PI/IN/2023/01 dated 09-Aug-2023

Adapted from Fluticasone furoate/Umeclidinium/Vilanterol GDS v11 / TRELEGY IPI v12 dated 28-Mar-2022.