

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TRELEGY ELLIPTA 100/62.5/25 fluticasone furoate (100 micrograms)/umeclidinium (as bromide) (62.5 micrograms)/vilanterol (as trifenate) (25 micrograms), powder for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 92 micrograms fluticasone furoate, 55 micrograms umeclidinium (equivalent to 65 micrograms umeclidinium [as bromide]) and 22 micrograms vilanterol (as trifenate).

This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 62.5 micrograms umeclidinium (equivalent to 74.2 micrograms umeclidinium bromide) and 25 micrograms vilanterol (as trifenate).

Excipient with known effect:

Each delivered dose contains approximately 25 milligrams of lactose (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for inhalation.

White powder in a light grey inhaler (Ellipta) with a beige mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TRELEGY ELLIPTA is indicated for the maintenance treatment of adults with moderate to severe chronic obstructive pulmonary disease (COPD) who require treatment with a long-acting muscarinic receptor antagonist (LAMA) + long-acting beta₂-receptor agonist (LABA) + inhaled corticosteroid (ICS).

TRELEGY ELLIPTA should not be used for the initiation of COPD treatment.

4.2. Dose and method of administration

Patients can be changed from their existing inhalers to TRELEGY ELLIPTA at the next dose. **However it is important that patients do not take other LABA or LAMA or ICS while taking TRELEGY ELLIPTA.**

A stepwise approach to the management of COPD is recommended, including the cessation of smoking and a pulmonary rehabilitation program. TRELEGY ELLIPTA is not to be used as initial therapy, but may be considered as step-up from LAMA/LABA or ICS/LABA or for patients already taking LAMA+LABA+ICS.

Dose

Adults

The recommended and maximum dose is one inhalation of TRELEGY ELLIPTA 100/62.5/25 once daily either morning or evening but at the same time every day. This equates to a maximum daily dose containing fluticasone furoate 100 micrograms, umeclidinium (as bromide) 62.5 micrograms, and vilanterol (as trifenate) 25 micrograms.

Special Populations

Elderly population

No dosage adjustment is required in patients over 65 years (see Section 5.2 Pharmacokinetic properties, Special Patient Populations).

Renal impairment

No dose adjustment is required for patients with renal impairment (see Section 5.2 Pharmacokinetic properties, Special Patient Populations).

Hepatic Impairment

No dosage adjustment is required in patients with hepatic impairment. Umeclidinium has not been studied in patients with severe hepatic impairment (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties, Special Patient Populations).

Paediatric population

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

Method of administration

TRELEGY ELLIPTA is for oral inhalation only. After inhalation, the patient should rinse their mouth with water without swallowing.

For instructions on the use and handling of this medicine, please refer to Section 6.6 Special precautions for disposal and other handling.

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

COPD

Treatment of COPD should be in accordance with relevant clinical guidelines. Patients should have a personal action plan designed in association with their treating physician.

Asthma

TRELEGY ELLIPTA should not be used in patients with asthma since it has not been studied in this population.

Pneumonia

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. In line with the known class effect of inhaled corticosteroids, pneumonia events (including pneumonias resulting in hospitalisation) were observed in patients with COPD receiving fluticasone furoate/umeclidinium/vilanterol. In some instances, fatal events of pneumonia have been reported with use of inhaled corticosteroid (fluticasone furoate)-containing drugs (see Section 4.8 Undesirable effects). Risk factors for pneumonia in patients with COPD receiving inhaled corticosteroid-containing drugs include current smoking status, history of pneumonia, low body mass index and severe COPD. These factors should be considered when TRELEGY ELLIPTA is prescribed, and treatment re-evaluated if pneumonia occurs.

Exacerbations

TRELEGY ELLIPTA is intended for the maintenance treatment of COPD. It should not be used for the relief of acute symptoms, i.e. as rescue therapy for the treatment of acute episodes of bronchospasm. Acute symptoms should be treated with an inhaled short-acting bronchodilator.

Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop therapy with TRELEGY ELLIPTA without physician supervision since symptoms may recur after discontinuation.

Paradoxical bronchospasm

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

Cardiovascular effects

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

Patients with hepatic impairment

Patients with moderate to severe hepatic impairment receiving TRELEGY ELLIPTA should be monitored for systemic corticosteroid-related adverse reactions (see Section 5.2 Pharmacokinetic properties, Special Patient Populations).

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 Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, cataract, glaucoma, central serous chorioretinopathy (CSCR) and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression.

Inhaled corticosteroids should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Antimuscarinic activity

Consistent with its antimuscarinic activity, TRELEGY ELLIPTA should be used with caution in patients with narrow-angle glaucoma or urinary retention. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g. eye pain or discomfort, blurred vision, visual halos or coloured images in association with red eyes from conjunctival congestion and corneal oedema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

Paediatric Population

TRELEGY ELLIPTA should not be used in children.

Elderly population

There are no special precautions for use in the elderly.

4.5. Interaction with other medicines and other forms of interaction

Clinically significant drug interactions mediated by fluticasone furoate, umecclidinium (as bromide) or vilanterol (as trifenate) 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 beta₂-adrenergic agonists, such as vilanterol. Concurrent use of both non-selective and selective beta-blockers should be avoided unless there are compelling reasons for their use.

Interaction with CYP3A4 inhibitors

Fluticasone furoate and vilanterol are both 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 will be increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see Section 5.2 Pharmacokinetic properties).

Interaction with P-glycoprotein inhibitors

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.

Interaction with CYP2D6 inhibitors

Umeclidinium is a substrate of CYP2D6. 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) was observed following repeat daily inhaled dosing to normal and CYP2D6-poor metaboliser subjects.

Interaction with sympathomimetic medicinal products

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of TRELEGY ELLIPTA. TRELEGY ELLIPTA should not be used in conjunction with other LABAs or medicinal products containing LABAs.

Interaction with monoamine oxidase inhibitors and tricyclic antidepressants

Vilanterol, like other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Other LAMAs and LABAs

Co-administration of TRELEGY ELLIPTA with other LAMAs or LABAs has not been studied and is not recommended as it may potentiate the adverse reactions (see Section 4.8 Undesirable effects and Section 4.9 Overdose).

4.6. Fertility, pregnancy and lactation

Pregnancy

There are insufficient data from the use of fluticasone furoate/umeclidinium/vilanterol in pregnant women. Corticosteroids and beta₂-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels (see Section 5.3 Preclinical safety data).

TRELEGY ELLIPTA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.

Breast-feeding

It is unknown whether fluticasone furoate, umeclidinium, vilanterol or their metabolites are excreted in human milk. However, other corticosteroids, muscarinic antagonists and beta₂-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.

Fertility

There are no data on the effects of TRELEGY ELLIPTA on human fertility. Studies in rats showed no effect of fluticasone furoate, umeclidinium or vilanterol on male or female fertility at doses of the individual agents producing large or very large multiples of the systemic exposure in humans.

4.7. Effects on ability to drive and use machines

There have been no studies to investigate the effect of fluticasone furoate/umeclidinium/vilanterol 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 (as bromide) or vilanterol (as trifenate) at clinical doses.

4.8. Undesirable effects

Summary of the safety profile

Clinical trial data

The safety profile of TRELEGY ELLIPTA (fluticasone furoate/umeclidinium/vilanterol) is based on data from three phase III clinical studies.

The first study included safety data from 911 patients with COPD who received doses of fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 micrograms once daily for up to 24 weeks, of whom 210 patients received fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 micrograms once daily for up to 52 weeks, with an active comparator, budesonide/formoterol 400/12 micrograms twice daily (Study CTT116853, FULFIL).

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

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

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

Adverse events following 24 weeks of treatment are presented in Table 1. This trial had no placebo treatment group.

Table 1. Adverse Events with ≥1% Incidence with TRELEGY ELLIPTA following 24 Weeks of Treatment

Adverse Event (Preferred Term)	Number (%) of Subjects	
	FF/UMEC/VI 100/62.5/25 mcg OD (n = 911)	BUD/FOR 400/12 mcg BD (n = 899)
Infections and Infestations		
Nasopharyngitis	64 (7)	43 (5)
Upper respiratory tract infection	20 (2)	19 (2)
Pneumonia	19 (2)	7 (<1)
Pharyngitis	15 (2)	9 (1)
Rhinitis	10 (1)	11 (1)
Influenza	10 (1)	8 (<1)
Nervous system disorders		
Headache	44 (5)	53 (6)
Musculoskeletal and connective tissue disorders		
Back pain	19 (2)	18 (2)
Arthralgia	17 (2)	13 (1)
Respiratory, thoracic, and mediastinal disorders		
Chronic obstructive pulmonary disease	15 (2)	23 (3)
Cough	10 (1)	10 (1)

BD = twice daily; BUD = budesonide; FOR = formoterol; OD = once daily;
FF/UMEC/VI = fluticasone furoate/umeclidinium/vilanterol (TRELEGY ELLIPTA)

In a subset of subjects, in addition to adverse events reported in Table 1, adverse events occurring at a rate of greater than or equal to 1% in subjects receiving fluticasone furoate/umeclidinium/vilanterol for up to 52 weeks (n = 210) were viral respiratory tract infection, oropharyngeal pain and hypertension.

Tabulated list of adverse reactions

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

- Very common: ≥1/10
- Common: ≥1/100 to <1/10
- Uncommon: ≥1/1000 to <1/100
- Rare: ≥1/10000 to <1/1000
- Very rare: <1/10000

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 Section 4.4 Special warnings and precautions for use)*

In Study CTT116853 which had a total of 1,810 patients with COPD FEV₁ 45% of predicted (standard deviation [SD] 13%) (mean post-bronchodilation), 65% of whom had experienced a moderate/severe COPD exacerbation in the year prior to study entry, a higher incidence of pneumonia events was reported in patients receiving fluticasone furoate/umeclidinium/vilanterol (20 patients, 2%) than in patients receiving budesonide/formoterol (7 patients, <1%). Pneumonia which required hospitalisation occurred in 1% of patients receiving fluticasone furoate/umeclidinium/vilanterol and <1% of patients receiving budesonide/formoterol up to 24 weeks. One fatal case of pneumonia was reported in a patient who received fluticasone furoate/umeclidinium/vilanterol, however this was not considered to be related to the study treatment. However, in the subset of 430 patients treated for up to 52 weeks, the incidence of pneumonia events reported in the fluticasone furoate/umeclidinium/vilanterol 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 FEV₁ 46% of predicted, SD 15%) (study CTT116855), the incidence of pneumonia was 8% for fluticasone furoate/umeclidinium/vilanterol (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 fluticasone furoate/umeclidinium/vilanterol, 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.

Post-marketing data

System organ class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and rash	Rare

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: <https://nzphvc.otago.ac.nz/reporting/>.

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 Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties).

Treatment

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

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

Further management should be as clinically indicated.

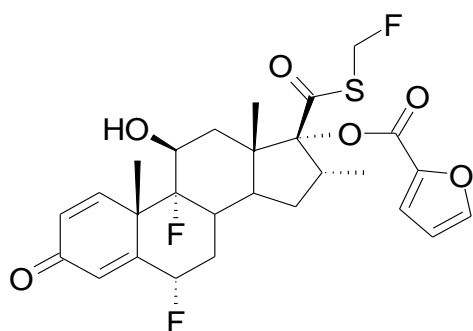
For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

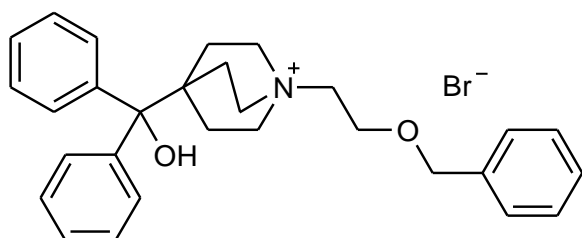
5.1. Pharmacodynamic properties

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

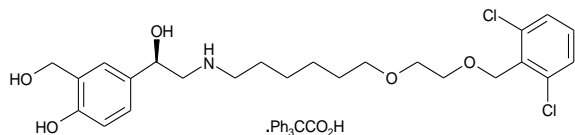
Structure of fluticasone furoate



Structure of umeclidinium (as bromide)



Structure of vilanterol (as trifenate)



Chemical Name

The chemical name of fluticasone furoate is androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-17-[(2-furanylcarbonyloxy)-11-hydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6 α ,11 β ,16 α ,17 α)- (9Cl)

The chemical name of umeclidinium (as bromide) is 1-Azoniabicyclo[2.2.2]octane, 4-(hydroxydiphenylmethyl)-1-[2-(phenylmethoxy)ethyl]-, bromide (1:1)

The chemical name of vilanterol (as trifenate) is benzeneacetic acid, α,α -diphenyl-, compd. with (α 1R)- α 1-[[[6-[2-[(2,6-dichlorophenyl)methoxy]ethoxy]hexyl]amino]methyl]-4-hydroxy-1,3-benzene dimethanol (1:1)

Molecular Formula

Fluticasone furoate: C₂₇H₂₉F₃O₆S

Umeclidinium (as bromide): C₂₉H₃₄BrNO₂

Vilanterol (as trifenate): $C_{24}H_{33}Cl_2NO_5 \cdot C_{20}H_{16}O_2$

CAS Number

Fluticasone furoate: 397864-44-7

Umeclidinium (as bromide): 869113-09-7

Vilanterol (as trifenate): 503070-58-4

Physicochemical properties

Fluticasone furoate is practically insoluble or insoluble in water, and slightly soluble in acetone, dimethylsulphoxide and ethanol.

Umeclidinium (as bromide) is slightly soluble in water and slightly soluble in methanol, ethanol, acetonitrile and propan-1-ol.

Vilanterol (as trifenate) is practically insoluble or insoluble in water and slightly soluble in methanol, ethanol, acetonitrile and propan-2-ol.

Mechanism of action

Fluticasone furoate, umeclidinium (as bromide) and vilanterol (as trifenate) represent three classes of medications: a synthetic corticosteroid (presented here as an inhaled corticosteroid [ICS]), a long-acting muscarinic receptor antagonist (also referred to as a LAMA) and a selective, long-acting beta₂-receptor agonist (also referred to as a LABA), respectively.

Fluticasone furoate

Fluticasone furoate is a synthetic trifluorinated 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 (as bromide)

Umeclidinium (as bromide) is a LAMA. It is a quinuclidine derivative that is a muscarinic receptor antagonist with activity across multiple muscarinic cholinergic receptor subtypes. Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic acetylcholine receptors on airway smooth muscle. It demonstrates slow reversibility at the human M₃ muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Vilanterol (as trifenate)

Vilanterol (as trifenate) is a selective LABA.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including vilanterol (as trifenate), are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyses 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 the triple combination of fluticasone furoate/umeclidinium (as bromide)/vilanterol (as trifenate) (hereafter referred to as fluticasone furoate/umeclidinium/vilanterol or FF/UMEC/VI) 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 seen 30 minutes after administration with umeclidinium/vilanterol 500/100 micrograms. No clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) was observed.

In addition, no clinically significant effects of umeclidinium/vilanterol on cardiac rhythm were observed on 24-hour Holter monitoring in 281 patients who received umeclidinium/vilanterol 125/25 micrograms once daily for up to 12 months.

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 fluticasone furoate/umeclidinium/vilanterol for up to 24 weeks, or in the subset of 210 subjects exposed for up to 52 weeks.

Clinical efficacy and safety

Study 1

The efficacy of fluticasone furoate/umeclidinium/vilanterol (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 (compared to budesonide/formoterol [BUD/FOR]) with an extension up to 52 weeks in a subset of patients (Study CTT116853, FULFIL).

All patients were required to have a smoking history of at least 10 pack years; a post-salbutamol FEV₁/ FVC ratio <0.70; a clinical diagnosis of COPD, and a post-bronchodilator FEV₁ of <50% predicted normal or a post-bronchodilator FEV₁ <80% predicted normal and a history of ≥2 moderate exacerbations or one severe (hospitalised) exacerbation in the previous 12 months at screening. At screening, the mean post-bronchodilator FEV₁ was 45.5% predicted, and the mean reversibility was 8.17%. Approximately 55% of patients had a history of ≥2 moderate or ≥1 severe COPD exacerbations in the 12 months prior to screening.

FF/UMEC/VI 100/62.5/25 micrograms administered once daily demonstrated a statistically significant improvement in lung function (as defined by change from baseline trough FEV₁ at Week 24; co-primary endpoint) compared with BUD/FOR) 400/12 micrograms administered twice-daily (see Table 2).

FF/UMEC/VI 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, and also for respiratory symptoms measured using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) score and sub-scale scores over Weeks 21-24, and breathlessness measured using the Transitional Dyspnoea Index (TDI) focal score at Week 24 (see Table 2).

FF/UMEC/VI 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 (see Table 2).

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

	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
Primary endpoints				
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	-
Secondary endpoints				
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

	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
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	-
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	-
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 SGRQ Total Score at Week 24 ^{f, h}	50%	41%	-	1.41 ^b (1.16, 1.70) p<0.001

BID=twice daily; BUD=budesonide; FOR=formoterol; CI=confidence interval; FEV₁=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 fluticasone furoate/umeclidinium/vilanterol (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).

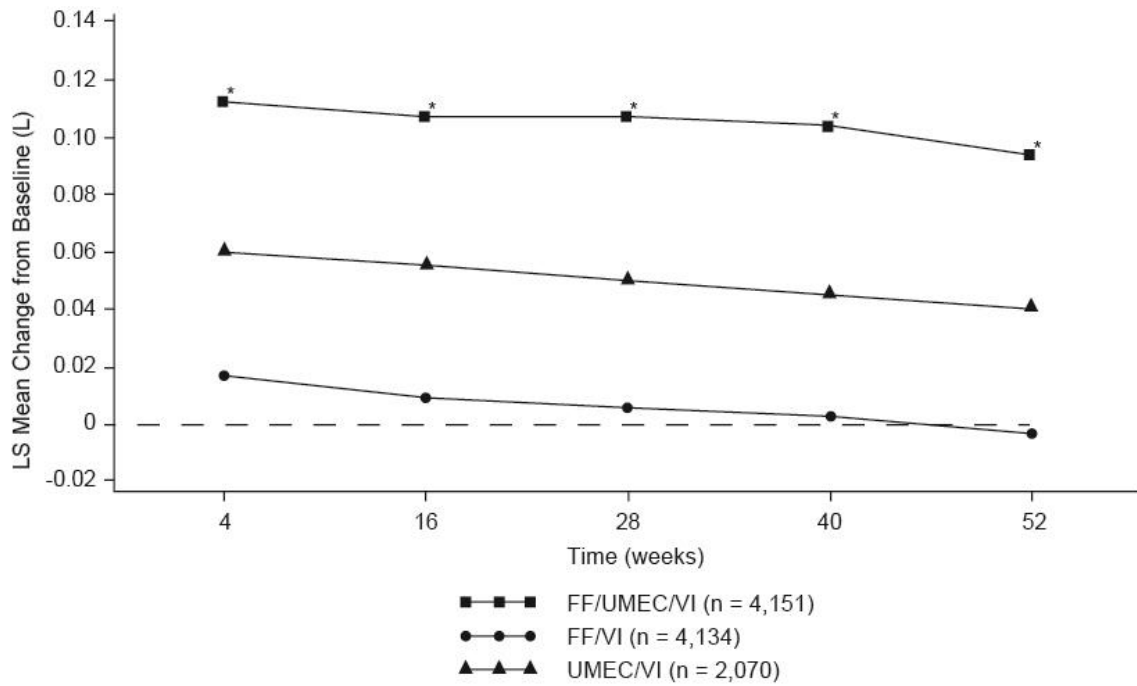
Patients treated with FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on-treatment moderate/severe exacerbations (primary endpoint) compared with FF/VI and compared with UMEC/VI. See Table 3 for efficacy endpoint results.

Table 3. Key efficacy endpoints (Study CTT116855)

	FF/UMEC/ VI (n = 4,151)	FF/VI (n = 4,134)	UMEC/VI (n = 2,070)	FF/UMEC /VI vs. FF/VI	FF/UMEC/ VI vs. UMEC/VI
Rate of Moderate/severe exacerbations^a					
Exacerbations per year	0.91	1.07	1.21		
Reduction in Rate (%)				15%	25%
95% CI				10, 20	19, 30
p-value				p<0.001	p<0.001
Time to first moderate/severe exacerbation					
Patients with an event (%)	47%	49%	50%		
Reduction in Risk (%)				14.8%	16.0%
95% CI				9.3, 19.9	9.4, 22.1
p-value				p<0.001	p<0.001
Rate of Severe exacerbations					
Exacerbations per year	0.13	0.15	0.19		
Reduction in Rate (%)				13%	34%
95% CI				-1, 24	22, 44
p-value				p=0.064	p<0.001
Trough FEV₁ (L) at Week 52					
LS mean change from baseline (SE)	0.094 (0.004)	-0.003 (0.004)	0.040 (0.006)		
Treatment difference				0.097	0.054
95% CI				0.085,	0.039,
p-value				0.109	0.069
				p<0.001	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				-1.8	-1.8
95% CI				-2.4, -1.1	-2.6, -1.0
p-value				p<0.001	p<0.001
Responders according to SGRQ Total Score at Week 52					
Responder ^b (%)	42%	34%	34%		
Odds Ratio				1.41	1.41
95% CI				1.29, 1.55	1.26, 1.57
p-value				p<0.001	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 FEV₁) of FF/UMEC/VI compared with FF/VI and UMEC/VI for trough FEV₁ 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 FEV1 (L)



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

The reduction in the mean number of occasions/day of beta₂-agonist rescue medication use and the percentage of 24-hour periods without need of rescue medication was statistically significant in patients receiving FF/UMEC/VI compared with FF/VI or UMEC/VI at Weeks 49 to 52 (see Table 4) and these differences were observed over the course of the 52-week study.

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

Table 4. Other endpoints (Study CTT116855)

	FF/UMEC/ VI (n = 4,151)	FF/VI (n = 4,134)	UMEC/VI (n = 2,070)	FF/UMEC/ VI vs. FF/VI	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				-0.28	-0.30
95% CI				-0.37, -0.19	-0.41, -0.19
p-value				p<0.001	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				5.2	4.4
95% CI				3.5, 6.9	2.3, 6.5
p-value				p<0.001	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				-0.05	-0.10
95% CI				-0.08, -0.01	-0.14, -0.05
p-value				p=0.005	p<0.001
CI=confidence interval; LS=least squared; n=number in the intent-to-treat population; SE=standard error.					

Treatment with FF/UMEC/VI 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 FF/UMEC/VI (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 FF/UMEC/VI (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 FF/UMEC/VI 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 FF/UMEC/VI (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 fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) (100/62.5/25 micrograms), administered as a single inhaler, with FF/VI (100/25 micrograms) + umeclidinium (62.5 micrograms), co-

administered as multi-inhaler therapy, once daily to patients with a history of moderate or severe exacerbations within the prior 12 months. In this study, FF/UMEC/VI was non-inferior compared with FF/VI + umeclidinium in the improvement from baseline in trough FEV₁ 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 FF/VI (100/25 micrograms) once daily in adult patients with a clinical diagnosis of COPD, resulted in statistically significant and clinically meaningful improvements in the primary endpoint of trough FEV₁ at Day 85 compared with placebo plus FF/VI (124 mL [95% CI: 93, 154; p<0.001] in Study 200109 and 122 mL [95% CI: 91, 152; p<0.001] in Study 200110).

5.2. Pharmacokinetic properties

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

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

Following inhaled administration of fluticasone furoate/umeclidinium/vilanterol 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 (as trifenate)

Following inhaled administration of fluticasone furoate/umeclidinium/vilanterol 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 dosing, fluticasone furoate is extensively distributed with an average volume of distribution at steady state of 661 L.

Fluticasone furoate has a low association with red blood cells. *In vitro* plasma protein binding in human plasma of fluticasone furoate was high, on average >99.6%. There was no decrease in the extent of *in vitro* plasma protein binding in subjects with renal or hepatic impairment.

Fluticasone furoate is a substrate for P-glycoprotein (P-gp), however, concomitant administration of fluticasone furoate with P-gp inhibitors is considered unlikely to alter fluticasone furoate systemic exposure. Clinical pharmacology studies with selective P-gp inhibitors and fluticasone furoate have not been conducted.

Umeclidinium (as bromide)

Following intravenous administration to healthy subjects, the mean volume of distribution was 86 L. *In vitro* plasma protein binding in human plasma was on average 89%.

Vilanterol (as trifenate)

Following intravenous administration to healthy volunteers, the mean volume of distribution at steady state was 165 L. *In vitro* plasma protein binding in human plasma was on average 94%.

Biotransformation

Fluticasone furoate

Based on *in vitro* data, the major routes of metabolism of fluticasone furoate in humans are mediated primarily by CYP3A4.

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.

A repeat-dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25 micrograms) and the strong CYP3A4 inhibitor ketoconazole (400 milligrams). 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 hour weighted mean serum cortisol.

Umeclidinium (as bromide)

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 (as trifenate)

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 beta₁- and beta₂- 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.

Elimination

Fluticasone furoate

Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Plasma clearance following intravenous administration was 65.4 L/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. Less than 1% of the recovered radioactive dose was eliminated in the urine. The apparent plasma elimination half-life following inhaled administration of fluticasone furoate was, on average, 24 hours.

Umeclidinium (as bromide)

Plasma clearance following intravenous administration was 151 L/hour. Following intravenous administration, approximately 58% of the administered radiolabelled dose (or 73% of the recovered radioactivity) was excreted in faeces by 192 hours post-dose. Urinary elimination accounted for 22% of the administered radiolabelled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration to healthy male subjects, total radioactivity was excreted primarily in faeces (92% of the administered radiolabelled dose or 99% of the recovered radioactivity) by 168 hours post-dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration. Umeclidinium plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3% to 4% drug excreted unchanged in urine at steady-state.

Vilanterol (as trifenate)

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

Special Patient Populations

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

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

Race

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

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

Elderly

Fluticasone furoate/umeclidinium/vilanterol has not been evaluated in elderly subjects. However, such studies have been conducted with fluticasone furoate/vilanterol and umeclidinium/vilanterol.

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

Renal impairment

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

A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30 mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or beta₂-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

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

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by AUC₍₀₋₂₄₎) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (Child-Pugh B) following repeat-dose administration (fluticasone furoate/vilanterol 200/25 micrograms) was associated with an average 34% reduction in

serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child-Pugh C) that received fluticasone furoate/vilanterol 100/12.5 micrograms, there was no reduction in serum cortisol (10% increase in serum cortisol).

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was no significant increase in systemic exposure to vilanterol (C_{max} and AUC) in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C).

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

Subjects with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC), and no evidence of altered protein binding by umeclidinium or decreased protein binding by vilanterol between subjects with moderate hepatic impairment and healthy volunteers was observed *in vitro*.

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

Other patient characteristics

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

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

5.3. Preclinical safety data

Genotoxicity

Fluticasone furoate was not genotoxic in a standard battery of studies, comprising bacterial mutation (Ames) assays, mouse lymphoma assay and rat bone marrow micronucleus tests.

Umeclidinium was not genotoxic in a standard battery of studies, comprising bacterial mutation assays, the mouse lymphoma tk assay and the rat bone marrow micronucleus test.

Vilanterol was negative in a complete battery of *in vitro* (Ames, UDS, SHE cell) assays and *in vivo* (rat bone marrow micronucleus) assays and equivocal in the mouse lymphoma assay. The weight of evidence suggests that vilanterol does not pose a genotoxic risk.

Carcinogenicity

No carcinogenicity studies were performed with the fluticasone furoate/umeclidinium/vilanterol combination.

Fluticasone furoate was not carcinogenic in lifetime inhalation studies in rats or mice at exposures 1.4 or 2.9 times higher, respectively, than in humans at 100 micrograms/day, based on AUC.

Umeclidinium was not carcinogenic in 2-year inhalation studies in mice or rats at doses yielding systemic exposure levels (plasma AUC) ≥ 20 - or ≥ 17 -fold the human clinical exposure of umeclidinium at the maximum recommended dose of 62.5 $\mu\text{g}/\text{day}$ in the respective species.

Proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland were observed in lifetime inhalation studies with vilanterol, consistent with findings for other β_2 -agonists. There was no increase in tumour incidence in rats or mice at exposures 0.9- or 22-fold, respectively, those at the maximum recommended human dose, based on AUC. These findings are not considered to indicate that vilanterol poses a carcinogenic hazard to patients.

Reproductive Toxicology

Fluticasone furoate was not teratogenic in studies by the inhalational route in rats and rabbits, but it caused decreased fetal weight and impaired ossification in rats (at 91 micrograms/kg/day) and abortion in rabbits (at doses of 47 micrograms/kg/day and greater), occurring in conjunction with maternotoxicity. There were no adverse effects on embryofetal development in rats at 23 micrograms/kg/day, yielding systemic exposure 6.6-fold the human clinical exposure at 100 micrograms fluticasone furoate based on AUC, and there were no developmental effects in a prenatal and postnatal study in rats (at doses up to 27 micrograms/kg/day).

Embryofetal development was unaffected by umeclidinium in rats treated at up to 278 micrograms/kg/day by inhalation (estimated to yield almost 50-fold the human clinical exposure at 62.5 micrograms per day) and in rabbits treated at up to 306 micrograms/kg/day by inhalation or up to 180 micrograms/kg/day subcutaneously (yielding approximately 32- and 180-fold the plasma AUC in patients). 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 (equivalent to approximately 61-fold the human clinical exposure at 62.5 micrograms umeclidinium, based on AUC).

In rabbits, there was evidence of maternal toxicity and embryotoxicity following inhalation exposure to vilanterol (as trifenate) at 591 and 62.7 micrograms/kg/day, respectively (equivalent to 64- and 6-fold the clinical exposure at 25 micrograms/day vilanterol, based on AUC). A non-dose related increase in malformations, including the rare open eyelid, was also observed. In a separate study with subcutaneous exposure, increased incidence of open eye and increase in skeletal variations (indicative of developmental delay) occurred at 300 micrograms/kg/day (equivalent to approximately 460-fold the clinical exposure at 25 micrograms/day vilanterol based on AUC) with a NOAEL of 30 micrograms/kg/day (equivalent to 62-fold the clinical exposure at 25 micrograms/day vilanterol based on AUC). Vilanterol had no adverse effect on pre- or post-natal development in rats.

Effect on Laboratory Tests

Interactions with laboratory tests have not been established.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (which contains milk protein)
Magnesium stearate

6.2. Incompatibilities

None.

6.3. Shelf life

2 years

In-use shelf-life

Following removal from the tray, the product may be stored for a maximum period of 1 month.

Write the date the inhaler should be discarded on the label in the space provided. The date should be added as soon as the inhaler has been removed from the tray.

6.4. Special precautions for storage

Store below 30°C.

If stored in the refrigerator, allow the inhaler to return to room temperature for at least 1 hour before use.

6.5. Nature and contents of container

TRELEGY ELLIPTA is a moulded plastic dry powder inhaler with a light grey body, a beige mouthpiece cover and a dose counter, packed in a foil tray containing a desiccant sachet. The tray is sealed with a peelable foil lid. The inhaler contains two strips of either 14 or 30 regularly distributed blisters, each containing a white powder.

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 (equivalent to 74.2 micrograms umeclidinium [as bromide]) and 25 micrograms of vilanterol (as trifenate).

Packs containing a single inhaler providing either 14 or 30 doses.

Not all pack sizes may be distributed in New Zealand.

6.6. Special precautions for disposal and other handling

Disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Instructions for handling

The Ellipta inhaler is provided in a foil laminate tray containing a desiccant sachet. The tray provides moisture protection and should only be opened when the patient is ready to inhale a dose. Once opened, the desiccant sachet should be discarded.

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

Important

The dose-counter indicates the number of doses left. Patients should consider getting a replacement when the counter shows the number 05. When the counter shows a full solid red background, it must be replaced.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900

Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
22 November 2018

10. DATE OF REVISION OF THE TEXT

16 April 2020

Summary table of changes:

Section changed	Summary of new information
4.8	Addition of hypersensitivity events in post-marketing section and ADR frequency changes

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Version 4.0