AUSTRALIAN PRODUCT INFORMATION

TRELEGY ELLIPTA 100/62.5/25 and 200/62.5/25 (fluticasone furoate/umeclidinium [as bromide]/vilanterol [as trifenatate]) powder for inhalation

1 NAME OF THE MEDICINE

Fluticasone furoate/umeclidinium (as bromide)/vilanterol (as trifenatate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each foil strip contains regularly distributed blisters with one strip containing either 100 micrograms or 200 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 trifenatate).

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

Excipients with known effect

Lactose monohydrate (which contains milk protein).

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

Asthma

TRELEGY ELLIPTA is indicated for the maintenance treatment of asthma in adult patients who are not adequately controlled with a combination of inhaled corticosteroid and a long-acting beta2-agonist.

COPD

TRELEGY ELLIPTA is indicated for the maintenance treatment of adults with moderate to severe COPD who require treatment with LAMA+LABA+ICS.

TRELEGY ELLIPTA is not indicated for the initiation of therapy in COPD.

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 long-acting beta$_2$-receptor agonists (LABA) or long-acting muscarinic receptor antagonists (LAMA) or inhaled corticosteroids (ICS) while taking TRELEGY ELLIPTA**.

Dose

Asthma

Patients should be made aware that TRELEGY ELLIPTA must be used regularly, even when asymptomatic.

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

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

Adults

The recommended dose is one inhalation of TRELEGY ELLIPTA 100/62.5/25 micrograms once daily or one inhalation of TRELEGY ELLIPTA 200/62.5/25 micrograms once daily.

TRELEGY ELLIPTA 100/62.5/25 micrograms should be considered for patients who require a low to mid dose of ICS in combination with a LAMA and a LABA.

TRELEGY ELLIPTA 200/62.5/25 micrograms should be considered for patients who require a higher dose of ICS in combination with a LAMA and a LABA.

If patients are inadequately controlled on TRELEGY ELLIPTA 100/62.5/25 micrograms, consider increasing the dose to 200/62.5/25 micrograms, which may provide additional improvement in asthma control.

Children and adolescents

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

COPD

A stepwise approach to the management of chronic obstructive pulmonary disease (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.

Adults

The recommended and maximum dose is one inhalation of TRELEGY ELLIPTA 100/62.5/25 once daily. This equates to a maximum daily dose containing fluticasone furoate

100 micrograms, umeclidinium (as bromide) 62.5 micrograms, and vilanterol (as trifenatate) 25 micrograms.

Children and adolescents

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

Asthma and COPD

Special populations

Elderly population

No dosage adjustment is required in patients over 65 years (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment

No dosage adjustment is required for patients with renal impairment (see Section 5.2 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES).

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.

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.

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 ADVERSE EFFECTS (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.

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

Exacerbations

TRELEGY ELLIPTA should not be used to treat acute asthma symptoms or an acute exacerbation in COPD for which an inhaled short-acting bronchodilator is required.

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

Patients should not stop therapy with TRELEGY ELLIPTA, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

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

Paradoxical bronchospasm

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

Cardiovascular effects

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

Patients with hepatic impairment

For patients with moderate to severe hepatic impairment receiving TRELEGY ELLIPTA, the 100/62.5/25 micrograms dose should be used, and patients should be monitored for systemic corticosteroid-related adverse reactions (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.2 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 Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression.

Ocular effects may be reported with systemic and topical corticosteroid use. If a patient presents with a change in vision, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR).

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.

Use in the elderly

There are no special precautions for use in the elderly.

Paediatric use

TRELEGY ELLIPTA should not be used in children or adolescents.

Effects on laboratory tests

Interactions with laboratory tests have not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinically significant drug interactions mediated by fluticasone furoate, umeclidinium (as bromide) or vilanterol (as trifenatate) 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. 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.

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.

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

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 enzyme. 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 $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular

system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

Other 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Section 4.9 OVERDOSE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in pregnancy

(Pregnancy Category B3)

There are insufficient data from the use of fluticasone furoate/umeclidinium/vilanterol in pregnant women. Corticosteroids and $beta_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels.

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 approximately 3-fold the human clinical exposure at 184 micrograms delivered dose of fluticasone furoate (the maximum recommended dose in patients with asthma) 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 40-fold the human clinical exposure at 55 micrograms delivered dose of umeclidinium 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 27- and 150-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 55 micrograms delivered dose of umeclidinium, based on AUC).

In rabbits, there was evidence of maternal toxicity and embryotoxicity following inhalation exposure to vilanterol (as trifenatate) at 591 and 62.7 micrograms/kg/day, respectively (equivalent to 118- and 10-fold the clinical exposure at 22 micrograms/day delivered dose of 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 845-fold the clinical exposure at 22 micrograms/day delivered dose of vilanterol based on AUC) with a NOAEL of 30 micrograms/kg/day (equivalent to 62-fold the clinical exposure at 22 micrograms/day

delivered dose of vilanterol based on AUC). Vilanterol had no adverse effect on pre- or post-natal development in rats.

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

Use in lactation

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

A decision must be made whether to discontinue breast-feeding or to discontinue TRELEGY ELLIPTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of 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 trifenatate) at clinical doses.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

The safety profile of TRELEGY ELLIPTA (fluticasone furoate/umeclidinium/vilanterol) is based on data from one phase III clinical study in asthma (205715) and two phase III clinical studies in COPD (CTT116853 and CTT116855).

Asthma

The asthma study (205715) included 2,436 adult subjects inadequately controlled on their current treatment of combination therapy (ICS plus a LABA) who received fluticasone furoate/umeclidinium/vilanterol or an active comparator of fluticasone furoate/vilanterol for 24 to 52 week's duration.

Study 1 (205715)

Adverse effects following 24 to 52 weeks of treatment with fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 micrograms or fluticasone furoate/umeclidinium/vilanterol 200/62.5/25 micrograms are presented in Table 1.

Table 1. Adverse Events with ≥1% Incidence with TRELEGY ELLIPTA (Study 205715)

Adverse Event (Preferred Term)	Number (%) of Subjects			
	FF/UMEC/VI 200/62.5/25 mcg (n = 408)	FF/UMEC/VI 100/62.5/25 mcg (n =406)	FF/VI 200/25 mcg (n = 406)	FF/VI 100/25 mcg (n = 407)
Infections and infestations				
Nasopharyngitis	51 (13)	60 (15)	53 (13)	63 (15)
Upper respiratory tract infection	19 (5)	15 (4)	13 (3)	21 (5)
Bronchitis	22 (5)	15 (4)	19 (5)	14 (3)
Viral respiratory tract infection	9 (2)	10 (2)	7 (2)	11 (3)
Sinusitis	12 (3)	6 (1)	9 (2)	9 (2)
Viral upper respiratory tract infection	9 (2)	6 (1)	11 (3)	6 (1)
Pharyngitis	9 (2)	9 (2)	14 (3)	8 (2)
Urinary tract infection	7 (2)	3 (<1)	1 (<1)	5 (1)
Rhinitis	6 (1)	10 (2)	8 (2)	11 (3)
Influenza	6 (1)	15 (4)	9 (2)	13 (3)
Pneumonia	3 (<1)	5 (1)	7 (2)	7 (2)
Respiratory tract infection	4 (<1)	6 (1)	3 (<1)	6 (1)
Nervous system disorders				
Headache	19 (5)	36 (9)	23 (6)	30 (7)
Musculoskeletal and connective tissue disorders				
Back pain	9 (2)	13 (3)	6 (1)	16 (4)
Respiratory, thoracic, and mediastinal disorders				
Dysphonia	6 (1)	6 (1)	8 (2)	5 (1)
Oropharyngeal pain	6 (1)	6 (1)	4 (<1)	4 (<1)
Cough	6 (1)	3 (<1)	6 (1)	5 (1)
Investigations				
Blood pressure increased	2 (<1)	5 (1)	5 (1)	1 (<1)
Vascular disorders				
Hypertension	5 (1)	8 (2)	8 (2)	9 (2)

COPD

The first study (CTT116853, FULFIL) included 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.

The second study (CTT116855, IMPACT) included 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, fluticasone furoate/vilanterol (FF/VI 100/25 micrograms) and umeclidinium/vilanterol (UMEC/VI 62.5/25 micrograms).

Study 1 (CTT116853)

Adverse events following 24 weeks of treatment are presented in Table 2.

Table 2. Adverse Events with ≥1% Incidence with TRELEGY ELLIPTA following 24 Weeks of Treatment (Study CTT116853)

Adverse Event (Preferred Term)	Number (%) of Subjects	
	FF/UMEC/VI 100/62.5/25 mcg OD (n=911)	BUD/FOR 400/12 mcg BID (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)

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

In a subset of subjects, in addition to adverse events reported in Table 2, 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.

Study 2 (CTT116855, IMPACT)

The most frequently reported adverse events are presented in Table 3.

Table 3. Adverse Events with ≥1% Incidence with TRELEGY ELLIPTA following 52 Weeks of Treatment (Study CTT116855)

Adverse Event (Preferred Term)	Number (%) of Subjects		
	FF/UMEC/VI 100/62.5/25 mcg (n=4,151)	FF/VI 100/25 mcg (n=4,134)	UMEC/VI 62.5/25 mcg (n=2,070)
Infections and Infestations			
Viral upper respiratory tract infection	521 (13)	479 (12)	223 (11)
Upper respiratory tract infection	299 (7)	283 (7)	117 (6)
Pneumonia	298 (7)	264 (6)	93 (4)
Bronchitis	152 (4)	130 (3)	73 (4)
Oral candidiasis	161 (4)	146 (4)	41 (2)
Influenza	117 (3)	102 (2)	50 (2)

Adverse Event (Preferred Term)	Number (%) of Subjects		
	FF/UMEC/VI 100/62.5/25 mcg (n=4,151)	FF/VI 100/25 mcg (n=4,134)	UMEC/VI 62.5/25 mcg (n=2,070)
Sinusitis	104 (3)	98 (2)	45 (2)
Urinary tract infection	92 (2)	86 (2)	35 (2)
Pharyngitis	82 (2)	81 (2)	48 (2)
Rhinitis	89 (2)	69 (2)	33 (2)
Psychiatric disorders			
Anxiety	46 (1)	28 (<1)	18 (<1)
Nervous system disorders			
Headache	233 (6)	198 (5)	103 (5)
Dizziness	54 (1)	36 (<1)	18 (<1)
Vascular disorders			
Hypertension	91 (2)	79 (2)	41 (2)
Respiratory, thoracic, and mediastinal disorders			
Chronic obstructive pulmonary disease	455 (11)	472 (11)	279 (13)
Cough	145 (3)	117 (3)	58 (3)
Dyspnoea	82 (2)	95 (2)	52 (3)
Oropharyngeal pain	99 (2)	71 (2)	39 (2)
Gastrointestinal disorders			
Diarrhoea	88 (2)	72 (2)	46 (2)
Constipation	65 (2)	63 (2)	16 (<1)
Abdominal pain	49 (1)	32 (<1)	18 (<1)
Skin and subcutaneous tissue disorders			
Rash	43 (1)	34 (<1)	16 (<1)
Musculoskeletal and connective tissue disorders			
Back pain	148 (4)	140 (3)	83 (4)
Arthralgia	122 (3)	86 (2)	46 (2)
Pain in extremity	52 (1)	53 (1)	26 (1)
Osteoarthritis	49 (1)	29 (<1)	12 (<1)
General disorders and administration site conditions			
Oedema peripheral	47 (1)	52 (1)	31 (1)
Pyrexia	49 (1)	37 (<1)	21 (1)

FF/UMEC/VI = fluticasone furoate/umeclidinium/vilanterol (TRELEGY ELLIPTA); FF/VI = fluticasone furoate/vilanterol; mcg = micrograms; UMEC/VI = umeclidinium/vilanterol.

Adverse reactions are listed by MedDRA system organ class and by frequency (see Table 4). Where adverse reaction frequencies differed between studies and populations, the higher frequency is reported. 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

T**able 4. Adverse Reactions with TRELEGY ELLIPTA**

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 tachyarrythmia 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)

COPD

In Study CTT116853 which had a total of 1,810 patients with COPD FEV_1 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 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 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.

Asthma

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

Post marketing data

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

Mechanism of action

Fluticasone furoate, umeclidinium (as bromide) and vilanterol (as trifenatate) 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 beta$_2$-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 asthma and COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines) involved in inflammation.

Umeclidinium (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 trifenatate)

Vilanterol (as trifenatate) is a selective LABA.

The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including vilanterol (as trifenatate), 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.

Pharmacodynamics

Cardiovascular effects

The effect of the triple combination of fluticasone furoate/umeclidinium (as bromide)/vilanterol (as trifenatate) (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 1,519 subjects with asthma exposed to fluticasone furoate/umeclidinium/vilanterol for up to 24 weeks, or in a subset of 364 subjects exposed for up to 52 weeks.

No clinically relevant effects on the QTc interval were observed on review of centrally-read ECGs from 911 subjects with COPD exposed to fluticasone furoate/umeclidinium/vilanterol for up to 24 weeks, or in a subset of 210 subjects exposed for up to 52 weeks.

Clinical trials

Asthma

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

This trial has a 5-week run-in/stabilisation period described as follows: subjects inadequately controlled [Asthma Control Questionnaire (ACQ-6) ≥1.5] on their current asthma treatment of inhaled corticosteroid (greater than fluticasone propionate 250 micrograms per day or equivalent) plus LABA entered a 3-week run-in period of treatment with fluticasone propionate/salmeterol 250/50 micrograms twice daily. Subjects who remained inadequately

controlled (ACQ-≥1.5) after the run-in period were transferred to fluticasone furoate/vilanterol (FF/VI) 100/25 micrograms once daily for a 2-week stabilisation period. Across all treatment groups, baseline demographics were similar.

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

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

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

The change from baseline in trough FEV_1 at Week 24 (primary efficacy endpoint) showed statistically significant improvements in lung function for both FF/UMEC/VI 100/62.5/25 micrograms and FF/UMEC/VI 200/62.5/25 micrograms compared with FF/VI 100/25 micrograms and FF/VI 200/25 micrograms, respectively (see Table 5, Figures 1 and 2).

Table 5. Lung function endpoints at Week 24 (Study 205715)

	FF/VI 100/25 (n=407)	**FF/UMEC/VI 100/62.5/25 (n=406)**	**FF/VI 200/25 (n=406)**	**FF/UMEC/VI 200/62.5/25 (n=408)**
Trough FEV_1 (L)				
LS mean change from baseline (SE)	0.024 (0.0157)	0.134 (0.0155)	0.076 (0.0156)	0.168 (0.0155)
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI p-value	Reference	0.110 0.066, 0.153 p<0.001	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI p-value	---	---	Reference	0.092 0.049, 0.135 p<0.001
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25[a] Treatment difference 95% CI	---	Reference	---	0.034 -0.009, 0.077

FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25[a] Treatment difference 95% CI	---	0.059 0.015, 0.102	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25[a] Treatment difference 95% CI	Reference	---	---	0.143 0.100, 0.187
FEV_1 at 3 hours post dose[b] (L)				
LS mean change from baseline (SE)	0.132 (0.0160)	0.243 (0.0158)	0.168 (0.0159)	0.286 (0.0158)
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI	Reference	0.111 0.067, 0.155	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI	---	---	Reference	0.118 0.074, 0.162
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Treatment difference 95% CI	---	Reference	----	0.044 0.000, 0.087
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI	---	0.075 0.031, 0.119	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI	Reference	---	---	0.155 0.110, 0.199
Trough FEV_1 Responder[b, c] (%)	32%	49%	37%	51%
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Odds Ratio 95% CI	Reference	2.16 1.61, 2.88	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Odds Ratio 95% CI	---	---	Reference	1.82 1.37, 2.41
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25[a] Odds Ratio 95% CI	---	Reference	---	1.08 0.82, 1.43
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25[a]				

Odds Ratio 95% CI	---	1.68 1.26, 2.23	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25[a] Odds Ratio 95% CI	Reference	---	---	2.33 1.74, 3.11

CI=confidence interval; FEV_1=forced expiratory volume in 1 second; L=litres; LS=least squared; n=number in the intent-to-treat population; SE=standard error

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

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

[c] Responder defined as >=100mL improvement from baseline

Figure 1. Least Squares (LS) Mean Change from Baseline in Trough FEV_1 (L) for FF/UMEC/VI 100/62.5/25 micrograms

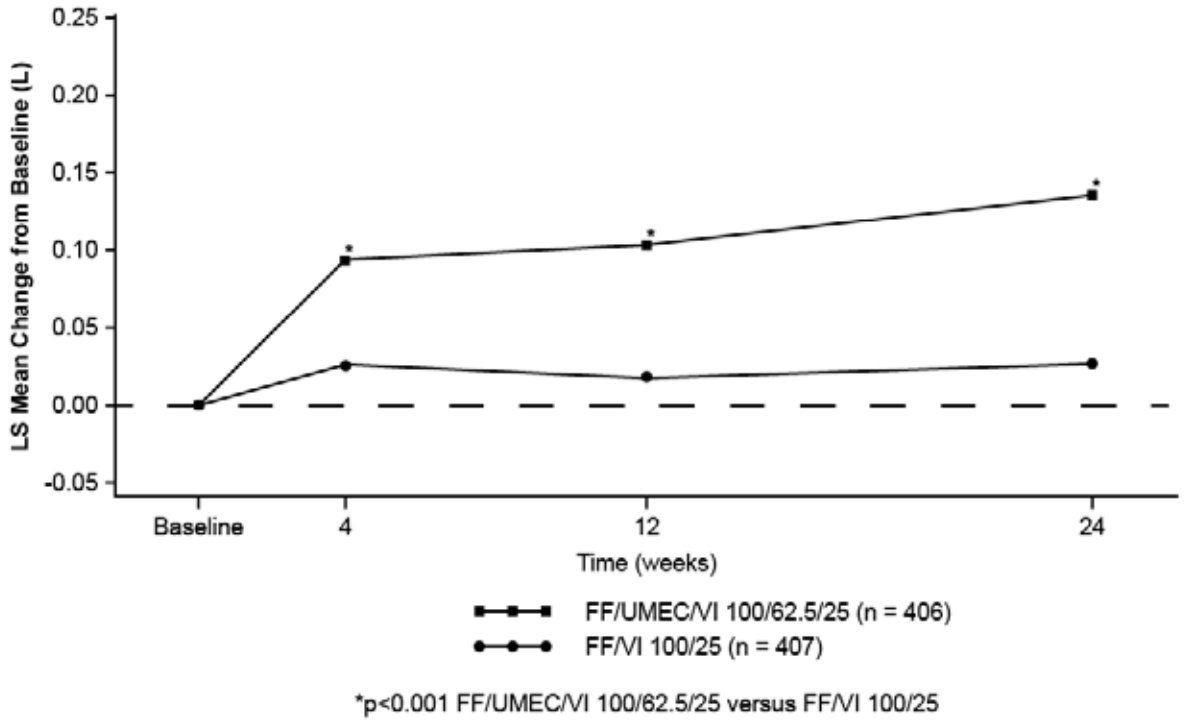
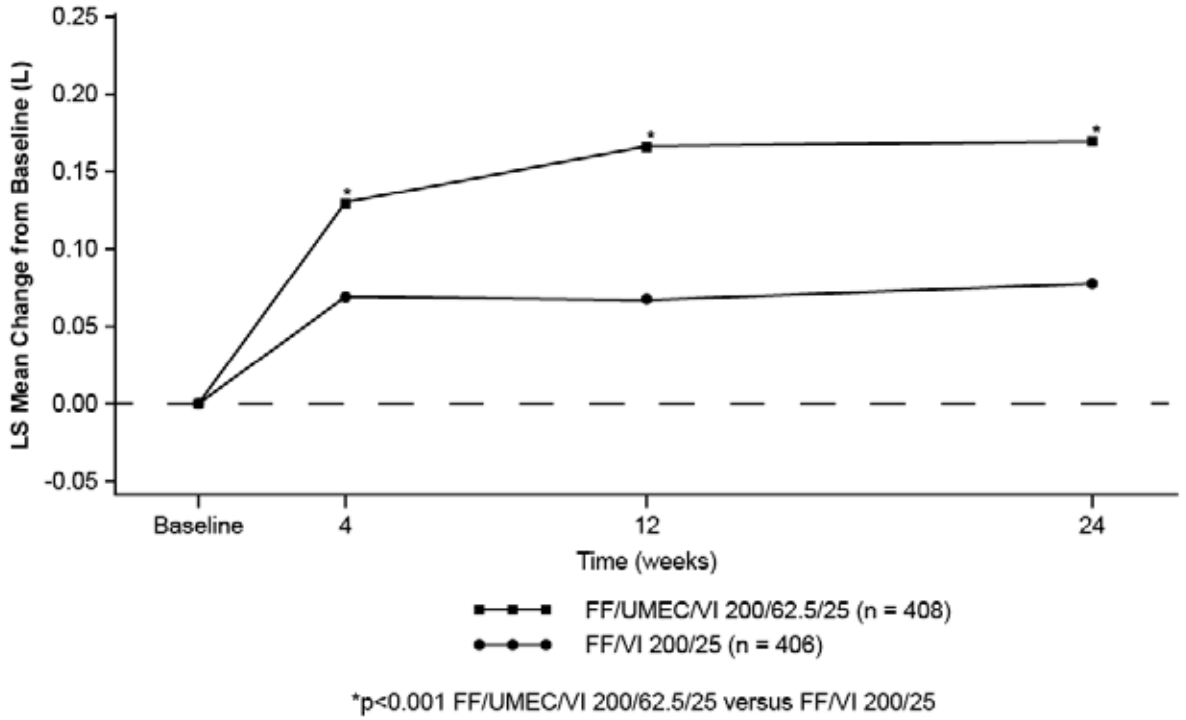


Figure 2. Least Squares (LS) Mean Change from Baseline in Trough FEV_1 (L) for FF/UMEC/VI 200/62.5/25 micrograms



Moderate/severe asthma exacerbations were assessed over the 52-week treatment period (see Table 6). In the pooled analysis, the annualised rate of moderate/severe exacerbations was numerically lower with FF/UMEC/VI (100/62.5/25 and 200/62.5/25 micrograms) compared with FF/VI (100/25 and 200/25 micrograms) (13% reduction in rate; 95% CI: -5.2, 28.1). Descriptive analyses of unpooled treatment comparisons for the annualised rate of moderate/severe exacerbations are also provided.

Table 6. Annualised Rate of Moderate/Severe Exacerbations[a] (Up to 52 Weeks) (Study 205715)

	FF/VI 100/25 (n=407)	**FF/UMEC/VI 100/62.5/25 (n=406)**	**FF/VI 200/25 (n=406)**	**FF/UMEC/VI 200/62.5/25 (n=408)**
Mean Annualised Rate	0.87	0.68	0.57	0.55
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Reduction in Rate (%) 95% CI	Reference	21.8% -1.1,39.5	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Reduction in Rate (%) 95% CI	---	---	Reference	3.2% -28.2, 27.0

FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Reduction in Rate (%) 95% CI	---	Reference	---	19.1% -6.4, 38.5
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Change in Rate (%) 95% CI	---	-19.6%[b] -57.2, 9.0	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Reduction in Rate (%) 95% CI	Reference	---	---	36.7% 17.6, 51.5
CI=confidence interval; n=number in the intent-to-treat population. [a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity. [b] Negative percentage reflects an increase in exacerbation rate for FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25.				

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

The mean annualised rates of severe exacerbations were 0.41 and 0.23 for FF/UMEC/VI 100/62.5/25 micrograms and FF/UMEC/VI 200/62.5/25 micrograms, respectively. The mean annualised rates of severe exacerbations were 0.38 and 0.26 for FF/VI 100/25 micrograms and FF/VI 200/25 micrograms, respectively.

Patient symptoms and health-related quality of life were assessed using the ACQ (see Table 7). In a descriptive pooled analysis, the treatment difference for the ACQ-7 change from baseline at Week 24 for FF/UMEC/VI (100/62.5/25 and 200/62.5/25) compared with FF/VI (100/25 and 200/25) was -0.089 (-0.156, -0.023). The ACQ-7 responder rate was 63% for FF/UMEC/VI (100/62.5/25 and 200/62.5/25 micrograms) compared with 55% for FF/VI (100/25 and 200/25 micrograms) at Week 24 (OR: 1.43; 95% CI: 1.16, 1.76). Descriptive analyses of unpooled treatment comparisons are also provided.

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

	FF/VI 100/25 (n=407)	**FF/UMEC/VI 100/62.5/25 (n=406)**	**FF/VI 200/25 (n=406)**	**FF/UMEC/VI 200/62.5/25 (n=408)**
Responder[b] (%)	52%	62%	58%	64%
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Odds Ratio 95% CI	Reference	1.59 1.18, 2.13	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Odds Ratio	---	---	Reference	1.28

95% CI				0.95, 1.72
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Odds Ratio 95% CI	---	Reference	---	1.08 0.80, 1.45
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Odds Ratio 95% CI	---	1.19 0.88, 1.60	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Odds Ratio 95% CI	Reference	---	---	1.71 1.27, 2.30
Change from Baseline[a]				
LS mean change from baseline (SE)	-0.638 (0.0340)	-0.754 (0.0335)	-0.717 (0.0339)	-0.779 (0.0339)
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI	Reference	-0.116 -0.210, -0.023	---	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI	---	---	Reference	-0.062 -0.156, 0.032
FF/UMEC/VI 200/62.5/25 vs. 100/62.5/25 Treatment difference 95% CI	---	Reference	---	-0.025 -0.118, 0.068
FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25 Treatment difference 95% CI	---	-0.037 -0.130, 0.057	Reference	---
FF/UMEC/VI 200/62.5/25 vs. FF/VI 100/25 Treatment difference 95% CI	Reference	---	---	-0.142 -0.236, -0.047
CI=confidence interval; n=number in the intent-to-treat population. [a] These comparisons were not in the predefined testing hierarchy and were not adjusted for multiplicity. [b] Defined as an ACQ- .				

The ACQ-5 (comprising the 5 questions on symptoms from ACQ-7) results at Week 24 were similar to the ACQ-7 results. In a pooled descriptive analysis, the treatment difference for the ACQ-5 change from baseline for FF/UME/VI (100/62.5/25 and 200/62.5/25) compared with FF/VI (100/25 and 200/25) was -0.043 (-0.121, 0.035). The ACQ-5 responder rate was 64% for FF/UMEC/VI (100/62.5/25 and 200/62.5/25 micrograms) compared with 60% for FF/VI (100/25 and 200/25 micrograms) (OR: 1.23; 95% CI: 1.00, 1.52) at Week 24.

In an unpooled descriptive analysis, the treatment difference for the ACQ-5 change from baseline at Week 24 for FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 was -0.080 (-

0.189, 0.030) and for FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 was -0.006 (-0.116, 0.103). The ACQ-5 responder rate was 63% for FF/UMEC/VI 100/62.5/25 micrograms compared with 58% for FF/VI 100/25 micrograms (OR: 1.28; 95% CI: 0.96, 1.72) at Week 24. The ACQ-5 responder rate was 66% for FF/UMEC/VI 200/62.5/25 micrograms compared with 62% for FF/VI 200/25 micrograms (OR: 1.19, 95% CI: 0.88, 1.60) at Week 24.

COPD

Study 1 (CTT116853, FULFIL)

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

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 FEV_1 at Week 24; co-primary endpoint) compared with BUD/FOR 400/12 micrograms administered twice-daily (see Table 8).

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 8).

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 8).

Table 8. 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 FEV1 (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
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

	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

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 (CTT116855, IMPACT)

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) (randomisation 2:2:1). At screening, approximately 90% of patients were using medications to control COPD: 34% triple therapy (ICS + LABA + LAMA), 26% combined ICS and LABA, 8% combined LAMA and LABA, 7% LAMA and 2% LABA monotherapy.

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 9 for efficacy endpoint results.

Table 9. 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
Primary endpoint					
Rate of moderate/severe exacerbations					
Exacerbations per year	0.91	1.07	1.21		
Absolute Risk Reduction (95% CI)				0.16 (0.11, 0.22)	0.30 (0.23, 0.37)

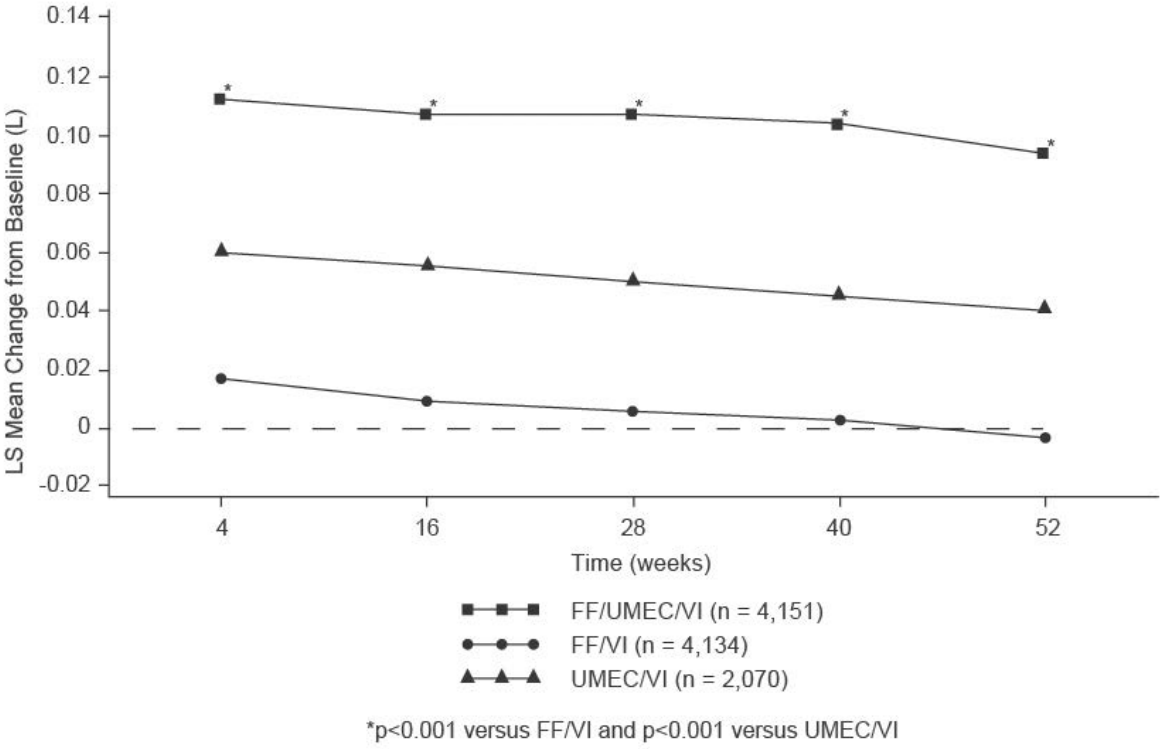
	FF/UMEC/VI (n=4,151)	FF/VI (n=4,134)	UMEC/VI (n=2,070)	FF/UMEC/VI vs. FF/VI	FF/UMEC/VI vs. UMEC/VI
Reduction in rate (%) 95% CI p-value				15% 10, 20 p<0.001	25% 19, 30 p<0.001
Secondary endpoints					
Time to first moderate/severe exacerbation					
Patients with an event (%)	47%	49%	50%		
Reduction 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		
Absolute Risk Reduction (95% CI)				0.02 (0.00, 0.04)	0.07 (0.04, 0.09)
Reduction in rate (%) 95% CI p-value				13% -1, 24 ns	34% 22, 44 p<0.001
Trough FEV_1 (L) at Week 52					
LS mean change from baseline (SE)	0.094 (0.004)	-0.003 (0.004)	0.040 (0.006)		
Treatment difference 95% CI p-value				0.097 0.085, 0.109 p<0.001	0.054 0.039, 0.069 p<0.001
SGRQ Total Score at Week 52					
LS mean change from baseline (SE)	-5.5 (0.23)	-3.7 (0.24)	-3.7 (0.35)		
Treatment difference 95% CI p-value				-1.8 -2.4, -1.1 p<0.001	-1.8 -2.6, -1.0 p<0.001
Responders according to SGRQ Total Score at Week 52					
Responder [a] (%)	42%	34%	34%		
Odds Ratio 95% CI p-value				1.41 1.29, 1.55 p<0.001	1.41 1.26, 1.57 p<0.001

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

[a] 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 FF/UMEC/VI compared with FF/VI and UMEC/VI for trough FEV_1 were observed at all timepoints over the course of the 52-week study (see Figure 3).

Figure 3. Least Squares (LS) Mean Change from Baseline in Trough FEV_1 (L)



Other supporting efficacy studies

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).

5.2 PHARMACOKINETIC PROPERTIES

When fluticasone furoate, umeclidinium (as bromide) and vilanterol (as trifenatate) 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 umeclidinium monotherapy.

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

the range of those observed following administration of umeclidinium 62.5 micrograms as monotherapy.

Population PK analyses for fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 micrograms were conducted using a combined dataset from three, phase III studies in 821 COPD subjects. Based on data from this analysis and historical datasets, systemic drug levels (steady state C_{max} and AUC_{0-24}) of fluticasone furoate, umeclidinium (as bromide) and vilanterol (as trifenatate) following fluticasone furoate/umeclidinium/vilanterol in one inhaler (triple combination) were within the range of those observed following fluticasone furoate/vilanterol + umeclidinium as 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 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 (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 trifenatate)

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 trifenatate)

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%.

Metabolism

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.

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 Cmax 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 trifenatate)

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.

Excretion

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 trifenatate)

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 the asthma population pharmacokinetic analyses (1,265 subjects for fluticasone furoate; 1,263 subjects for vilanterol; 634 subjects for umeclidinium), the impact of demographic covariates (race/ethnicity, age, gender, weight) on the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol was evaluated. In a COPD population pharmacokinetic analysis (n = 821), the impact of demographic covariates (race/ethnicity, age, gender, weight) on the pharmacokinetics of fluticasone furoate, umeclidinium, and vilanterol was evaluated. Renal and hepatic impairment were assessed in separate studies.

Race

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

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

In 113 East Asian subjects with COPD (Japanese and East Asian heritage) who received FF/UMEC/VI 100/62.5/25 micrograms from a single inhaler (27% subjects), estimates of fluticasone furoate $AUC_{(0-24)}$ 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 were observed for subjects with asthma or COPD.

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 $beta_2$-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

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. 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 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). For patients with moderate or severe hepatic impairment the maximum dose is 100/62.5/25 micrograms (see Section 4.2 DOSE 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), 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 dose adjustment is required for fluticasone furoate, umeclidinium or vilanterol based on the effect of gender, weight or body mass index.

In terms of other patient characteristics, a study in 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 of 0.6- or 1.3-fold, respectively, than in humans at 184 micrograms delivered dose/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 55 micrograms delivered dose/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 $beta_2$-agonists. 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 22 micrograms delivered dose/day, based on AUC. These findings are not considered to indicate that vilanterol poses a carcinogenic hazard to patients.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate (which contains milk protein)
Magnesium stearate

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

Not all pack sizes and strengths may be distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

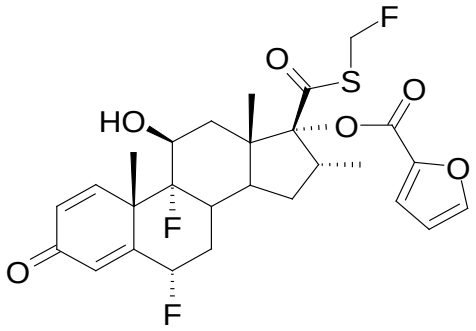
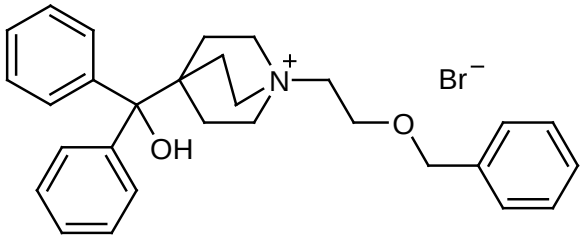
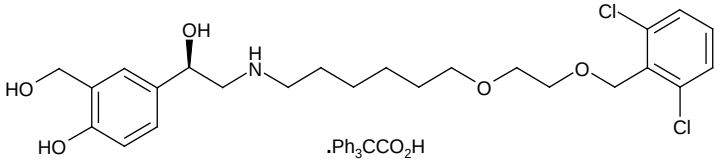
6.7 PHYSICOCHEMICAL PROPERTIES

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 trifenatate) is practically insoluble or insoluble in water and slightly soluble in methanol, ethanol, acetonitrile and propan-2-ol.

Chemical structure

Fluticasone furoate	
Chemical name	androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6 ,11 ,16 ,17)- (9Cl)
Molecular formula	$C_{27}H_{29}F_3O_6S$
Structure	
Umeclidinium (as bromide)	
Chemical name	1-Azoniabicyclo[2.2.2]octane, 4- (hydroxydiphenylmethyl)-1-[2-(phenylmethoxy)ethyl]-, bromide (1:1)
Molecular formula	$C_{29}H_{34}BrNO_2$
Structure	
Vilanterol (as trifenatate)	
Chemical name	benzeneacetic -diphenyl- - -[[[6-[2-[(2,6-dichlorophenyl)methoxy]ethoxy] hexyl]amino]methyl]-4-hydroxy-1,3-benzene dimethanol (1:1)
Molecular formula	$C_{24}H_{33}Cl_2NO_5.C_{20}H_{16}O_2$
Structure	

CAS number

Fluticasone furoate: 397864-44-7

Umeclidinium (as bromide): 869113-09-7

Vilanterol (as trifenatate): 503070-58-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4, 436 Johnston Street,
Abbotsford, Victoria 3067
Australia

9 DATE OF FIRST APPROVAL

16 January 2018

10 DATE OF REVISION

10 May 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	Addition of new 200/62.5/25 microgram strength
4.1	Addition of asthma indication
4.2	Addition of asthma dosing information and clarification of existing text
4.4	Addition of information related to asthma indication
4.8	Addition of information related to asthma indication
5.1	Addition of data for asthma indication
5.2	Addition of data for asthma indication
6.5	Update to statement regarding availability of different strengths in Australia
All	Minor editorial updates throughout the document

Version 5.0

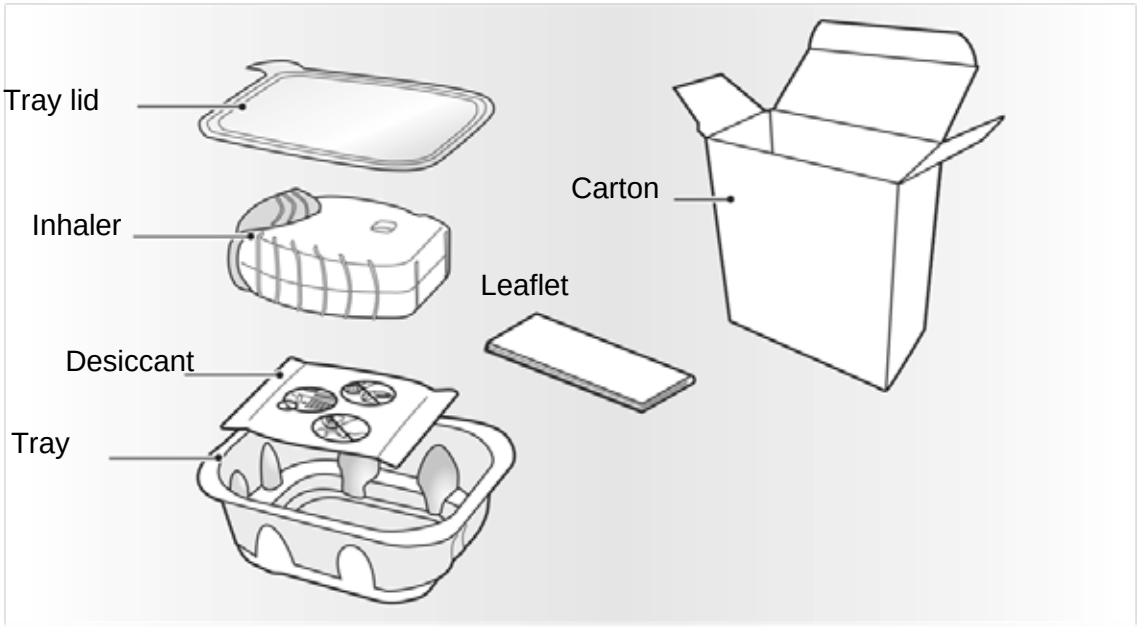
How to Use TRELEGY ELLIPTA

What is the Ellipta inhaler?

TRELEGY ELLIPTA is inhaled through the mouth using the Ellipta inhaler.

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 these step-by-step instructions.

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 — **do not** open, eat or inhale it.

When you take the inhaler out of the sealed tray, it will be in the 'closed' position. **Do not 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 open the tray. **After this date, the inhaler should no longer be used.**

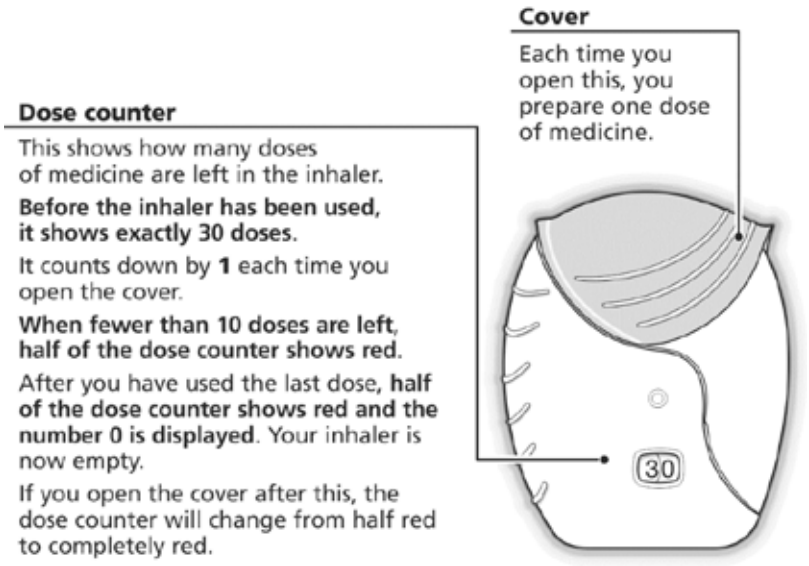
The step-by-step instructions shown below for the 30-dose (30-day supply) Ellipta inhaler also apply to the 14-dose (14-day supply) Ellipta inhaler.

Important information to read 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.

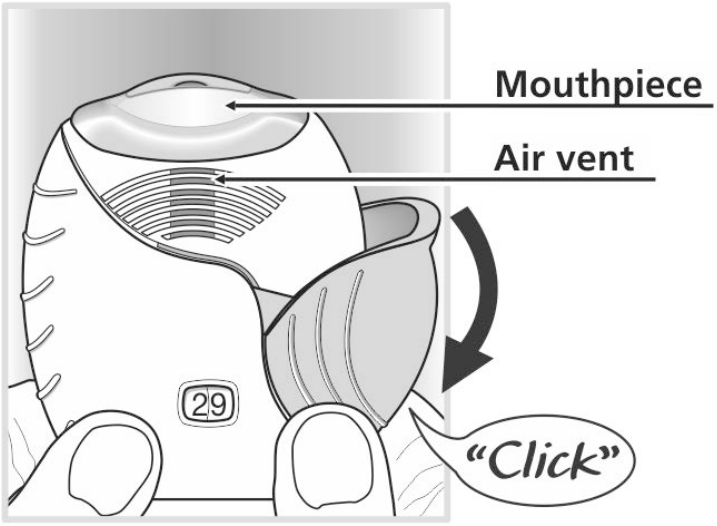


Step 1: Prepare a dose

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.

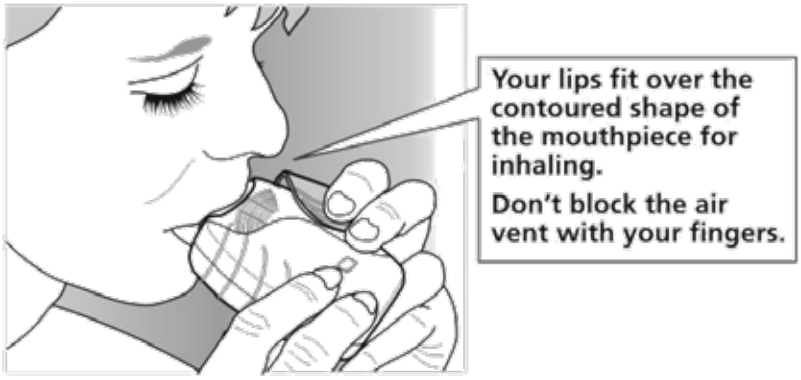
Step 2: Inhale your medicine

Whilst holding the inhaler away from your mouth, breathe out as far as is comfortable.

Do not breathe out into the inhaler.

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

Do not block the air vent with your fingers.



Take one long, steady, deep breath in. Hold this breath for about 3-4 seconds or for as long as is comfortable.

Remove the inhaler from your mouth.

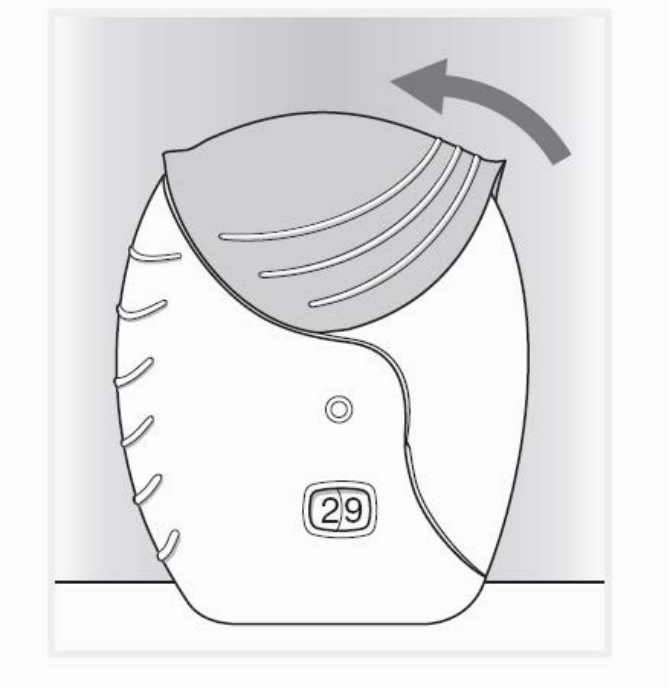
Breathe out slowly and gently away from the mouthpiece.

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.

Step 3: 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 without swallowing after you have used the inhaler.

This will make it less likely that you will develop a sore mouth or throat as side effects.