TRELEGY Ellipta

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

TRELEGY Ellipta

Powder for Inhalation

(Fluticasone furoate 100 µg/umeclidinium 62,5 µg/vilanterol 25 µg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each pre-dispensed dose contains 100 µg fluticasone furoate, 62,5 µg umeclidinium (equivalent to 74,2 µg umeclidinium bromide) and 25 µg vilanterol (as trifenatate). Each delivered dose (the dose leaving the mouthpiece of the inhaler) contains 92 µg fluticasone furoate, 55 µg umeclidinium (equivalent to 65 µg umeclidinium bromide) and 22 µg vilanterol (as trifenatate).

Contains sugar (lactose monohydrate (which contains milk protein) 25 mg/dose).

For full list of excipients, see section 6.1.

3. PHARMACUTICAL FORM:

Powder for Inhalation

The Ellipta inhaler contains two blister foil strips of 14 or 30 regularly distributed blisters, each containing a white powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

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

4.2 Posology and method of administration:

TRELEGY is for oral inhalation only.

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

Adults: The recommended and maximum dose is one inhalation of TRELEGY once daily, at the same time each day.

Children and adolescents: Use in patients less than 18 years of age is not relevant given the indication for TRELEGY.

Elderly: No dosage adjustment is required in patients over 65 years (see section 5.2).

Renal impairment: No dosage adjustment is required for patients with renal impairment (see section 5.2**)**.

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 and section 5.2).

4.3 Contraindications:

TRELEGY 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:

The use of TRELEGY has not been studied in patients with asthma and is not recommended in this patient population.

Exacerbations: TRELEGY 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 medical practitioner.
Patients should not stop therapy with TRELEGY without medical practitioner supervision since symptoms may recur after discontinuation.

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

Cardiovascular effects: Cardiovascular effects, such as cardiac dysrhythmias 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 should be used with caution in patients with unstable or life-threatening cardiovascular disease, or heart rhythm abnormalities***,*** hypothyroidism or uncorrected hypokalaemia.
Hypokalaemia may occur. Overdosages may cause cardiac effects. High dosages may increase the risk of serious side effects, including cardiac dysrhythmias. This risk is further aggravated if TRELEGY is administered concomitantly with other medicines that cause hypokalaemia and cardiac dysrhythmias, or in the presence of hypoxia and acidosis. The maximum dosage should not be exceeded.

Patients with hepatic impairment: Patients with moderate to severe hepatic impairment receiving TRELEGY should be monitored for systemic corticosteroid-related adverse reactions (see section 5.2).

Systemic corticosteroid effects: Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for maintenance treatment. Possible systemic effects include hypothalamic-pituitary-adrenal (HPA) suppression, decrease in bone mineral density, cataract, glaucoma and central serous chorioretinopathy (CSCR).

TRELEGY should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Antimuscarinic activity:

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

Pneumonia: In line with the known class effect of inhaled corticosteroids, pneumonia events (including pneumonias resulting in hospitalisation) were observed in patients with COPD receiving TRELEGY. In some instances, fatal events of pneumonia have been reported with use of inhaled corticosteroid fluticasone furoate-containing medicines, including TRELEGY (see section 4.8). Medical practitioners should remain vigilant for the possible development of pneumonia in patients with COPD, as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving inhaled corticosteroid-containing medicines include current smokers, patients with a history of prior pneumonia, patients with low body mass index and patients with severe COPD. These factors should be considered when TRELEGY is prescribed and treatment should be re-evaluated if pneumonia occurs.

Diabetic patients: There have been reports of increases in blood sugar levels in diabetic patients and this should be considered when prescribing TRELEGY to patients with a history of diabetes mellitus.

TRELEGY contains lactose: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption or fructose intolerance should not use TRELEGY (see section 1).

4.5 Interactions with other medicines and other forms of interaction:

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

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

Interaction with CYP3A4 inhibitors:

Fluticasone furoate and vilanterol, both components of TRELEGY, are rapidly cleared by extensive first-pass metabolism mediated by the enzyme CYP3A4.

Care is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see section 5.2).

Other long acting antimuscarinics and long acting beta$_2$- adrenergic agonists: Co-administration of TRELEGY with other long-acting muscarinic antagonists or long-acting beta$_2$-adrenergic agonists has not been studied and is not recommended as it may potentiate the adverse reactions (see section 4.8 and section 4.9).

4.6 Fertility, pregnancy and lactation:

Safety in pregnancy and lactation is not established.

Pregnancy: There are insufficient data from the use of TRELEGY in pregnant women. Animal studies have shown reproductive toxicity after administration of beta$_2$-agonists or corticosteroids.

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 breastfed newborns/infants cannot be excluded.

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

4.7 Effects on the ability to drive and use machines:

There have been no studies to investigate the effect of TRELEGY on the ability to perform tasks that require judgement, motor or cognitive skills.

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

4.8 Undesirable effects:

Clinical trial data:

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: ≥ 1/1 000 to < 1/100

Rare: ≥ 1/10 000 to < 1/1 000

Very rare: < 1/10 000.

Table 1 Adverse Reactions

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Pneumonia*	Common
	Upper respiratory tract infection	
	Bronchitis	
	Pharyngitis	
	Rhinitis	
	Sinusitis	
	Influenza	
	Nasopharyngitis	
	Candidiasis of mouth and throat	
	Urinary tract infection	
	Viral respiratory tract infection	Uncommon
Nervous system disorders	Headache	Common
	Dysgeusia	Uncommon
Eye disorders	Vision blurred (see section 4.4)	Uncommon

	Glaucoma Eye pain	
Cardiac disorders	Supraventricular tachyarrhythmia Tachycardia Atrial fibrillation	Uncommon
Respiratory, thoracic & mediastinal disorders	Cough Oropharyngeal pain Dysphonia	Common Uncommon
Gastrointestinal disorders	Constipation Dry mouth	Common Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia Back pain Fractures	Common Uncommon

Description of selected adverse reactions:

Pneumonia (see section 4.4):

In a total of 1 810 patients with advanced COPD (mean post bronchodilatory screening FEV1 45 % of predicted, SD 11 %), 65 % of which had experienced a moderate/severe COPD exacerbation in the year prior to study entry, there was a higher incidence of pneumonia events reported up to 24 weeks in patients receiving TRELEGY (20 patients, 2 %) than in patients receiving budesonide/formoterol (7 patients, < 1 %). Pneumonia which required hospitalisation occurred in 1 % of patients receiving TRELEGY and < 1 % of patients receiving budesonide/formoterol up to 24 weeks. One fatal case of pneumonia was reported in a patient who received TRELEGY. In the subset of 430 subjects treated for up to 52 weeks, the incidence of pneumonia events reported in both TRELEGY and budesonide/formoterol arms was equal at 2 %. The incidence of pneumonia events with TRELEGY is comparable with that observed in the FF/VI 100/25 arm of FF/VI clinical studies in COPD.

Post-marketing data:

System organ class	Adverse reaction(s)	Frequency

Immune system disorders	Hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, and rash	Less Frequent
Metabolism and nutrition disorders	Hyperglycaemia	Less Frequent
Psychiatric disorders	Anxiety	Less Frequent
Nervous system disorders	Tremor	Less Frequent
Eye disorders	Intraocular Pressure Increased	Less Frequent
Cardiac disorders	Palpitations	Less Frequent
Musculoskeletal and Connective tissue disorders	Muscle spasms	Less Frequent
Renal and urinary disorders	Urinary retention Dysuria	Less Frequent

Reporting of 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 providers are asked to report any suspected adverse reactions to SAHPRA via the **'6.04 Adverse Drug Reactions Reporting Form'**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

No data from clinical studies are available regarding overdose of TRELEGY.

Signs and Symptoms: An overdose of TRELEGY may produce signs, symptoms or adverse effects associated with the individual components' pharmacological actions (see section 4.4 and section 5.1).

Treatment: There is no specific treatment for an overdose with TRELEGY. 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 medicines should be used with caution in patients with a history of bronchospasm.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category A 21.5.1 Corticosteroids and analogues

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

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

Umeclidinium: Umeclidinium is a long-acting muscarinic receptor antagonist (also referred to as an anticholinergic). Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic cholinergic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Vilanterol: Vilanterol is a selective long acting beta$_2$-agonist (LABA). The pharmacologic effects of beta$_2$-adrenoceptor agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that 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.

Cardiovascular effects: The effect of fluticasone furoate/umeclidinium/vilanterol on the QT interval has not been evaluated in a thorough QT (TQT) study. TQT studies for FF/VI and UMEC/VI did not show clinically relevant effects on QT interval at clinical doses of FF, UMEC and VI (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 µg or 500/100 µg 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 to 6,4) milliseconds seen 10 minutes after administration with umeclidinium/vilanterol 125/25 µg and 8,2 (90 % CI = 6,2 to 10,2) milliseconds 30 minutes after administration with umeclidinium/vilanterol 500/100 µg. No clinically relevant effect on prolongation of QT interval (corrected using the Fridericia method) was observed at the umeclidinium/vilanterol 125/25 µg dose. In addition, no clinically significant effects of umeclidinium/vilanterol on cardiac rhythm were observed on 24-hour Holter monitoring in 281 patients who received umeclidinium/vilanterol 125/25 µg 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 µg and fluticasone furoate/vilanterol 800/100 µg, 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 µg and fluticasone furoate/vilanterol 800/100 µg, 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.

5.2 Pharmacokinetic Properties:

When fluticasone furoate (FF), umeclidinium (UMEC) and vilanterol (VI) 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 or umeclidinium/vilanterol combination.

Population PK analyses for FF/UMEC/VI were conducted in a subset of 74 COPD subjects from the phase III study. Systemic levels of FF, UMEC and VI following FF/UMEC/VI in one inhaler (triple combination) were within the range of those observed following dual combinations (FF/VI and UMEC/VI) as well as individual single inhalers (FF, UMEC and VI).

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: 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: 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 administration of fluticasone furoate to healthy subjects, the mean volume of distribution was 661 ℓ. *In vitro* plasma protein binding in human plasma was $>$ 99,6 %.

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

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

Metabolism:

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

Umeclidinium: *In vitro* studies showed that umeclidinium is metabolised principally by the enzyme P450 CYP2D6 and is a substrate for the P-gp transporter. The primary metabolic routes for umeclidinium are oxidative (hydroxylation, O-dealkylation) followed by conjugation (glucuronidation, etc), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low.

Vilanterol: *In vitro* studies showed that vilanterol is metabolised principally via CYP3A4 and is a substrate for the P-gp transporter. The primary metabolic routes are O-dealkylation to a range of metabolites with significantly reduced $beta_1$- and $beta_2$- agonist activity. Plasma metabolic profiles following oral administration of vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low.

Interactions:

A repeat dose study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25 µg) and ketoconazole (400 mg, a strong CYP3A4 inhibitor and Pgp inhibitor). Co-administration increased mean fluticasone furoate $AUC_{(0-24)}$ and C_{max} by 36 % and 33 %, respectively. The increase in fluticasone furoate exposure was associated with a 27 % reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol $AUC_{(0-t)}$ and C_{max} by 65 % and 22 %, respectively. The increase in vilanterol exposure was not associated with an increase in beta-agonist related systemic effects on heart rate or blood potassium.

Fluticasone furoate, umeclidinium and vilanterol are substrates of P-gp. A repeat dose drug interaction study performed in healthy subjects who were administered with umeclidinium/vilanterol or

umeclidinium, and the P-gp and moderate CYP3A4 inhibitor verapamil (240 mg), did not show any clinically significant effect on the pharmacokinetics of vilanterol or umeclidinium.

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

Elimination:

Fluticasone furoate: The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of fluticasone furoate/vilanterol was, on average, 24 hours. Following intravenous administration, the elimination phase half-life averaged 15,1 hours. Plasma clearance following intravenous administration was 65,4 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, with < 1 % of the recovered radioactive dose eliminated in the urine.

Umeclidinium: Umeclidinium plasma elimination half-life following inhaled dosing for 10 days averaged 19 hours, with 3 % to 4 % drug excreted unchanged in urine at steady-state. Plasma clearance following intravenous administration was 151 ℓ/hour. Following intravenous administration, approximately 58 % of the administered radiolabelled dose was excreted in faeces and approximately 22 % of the administered radiolabelled dose was excreted in urine. The excretion of the drug-related material in the faeces following intravenous dosing indicated secretion into the bile. Following oral administration, 92 % of the administered radiolabelled dose was excreted primarily in faeces. Less than 1 % of the orally administered dose (1 % of recovered radioactivity) was excreted in urine, suggesting negligible absorption following oral administration.

Vilanterol: Vilanterol plasma elimination half-life following inhaled dosing for 10 days averaged 11 hours. Plasma clearance of vilanterol following intravenous administration was 108 ℓ/hour. Following oral administration of radiolabelled vilanterol, 70 % of the radiolabel was excreted in urine

and 30 % in faeces. Primary elimination of vilanterol was by metabolism followed by excretion of metabolites in urine and faeces.

Special Patient Populations:

Race: In subjects with COPD, estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects (13-14 % subjects) were on average 23 % to 30 % higher compared with Caucasian subjects. However, there was no evidence for the higher systemic exposure in this population to be associated with greater effect on 24-hour urinary cortisol excretion. There was no effect of race on pharmacokinetics of umeclidinium or vilanterol in subjects with COPD.

Elderly: In studies with fluticasone furoate/vilanterol, there was no evidence for age to affect the PK of fluticasone furoate in subjects with COPD while there was an increase (37 %) in $AUC_{(0-24)}$ of vilanterol over the observed age range of 41 to 84 years. For an elderly subject (aged 84 years) with low bodyweight (35 kg) vilanterol $AUC_{(0-24)}$ is predicted to be 35 % higher than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg), whilst C_{max} is predicted to be unchanged. These differences are unlikely to be of clinical relevance.

A population pharmacokinetic analysis of COPD patients treated with umeclidinium/vilanterol showed that pharmacokinetics of umeclidinium and vilanterol were similar between COPD patients 65 years and older and those younger than 65 years of age.

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

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

A study in subjects with severe renal impairment administered with umeclidinium/vilanterol showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC). *In*

vitro protein binding studies between subjects with severe renal impairment and healthy volunteers were conducted, and no clinically significant evidence of altered protein binding was seen.

The effects of haemodialysis have not been studied.

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

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0–24)}$) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects.

The increase in fluticasone furoate systemic exposure (fluticasone furoate/vilanterol 200/25 µg) in subjects with moderate hepatic impairment (Child-Pugh B) was associated with an average 34 % reduction in serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child-Pugh C) that received fluticasone furoate/vilanterol 100/12,5 µg 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 µg) or with severe hepatic impairment (vilanterol, 12,5 µg) compared with healthy subjects.

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

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

Other patient characteristics:

Population pharmacokinetic analyses in COPD subjects treated with fluticasone furoate/vilanterol or umeclidinium/vilanterol showed that 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Lactose monohydrate and magnesium stearate.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage:

Store at or below 30 °C.

Store in the original package in order to protect from moisture and do not open the foil lid until ready for first use.

Following removal from the tray, the product may be stored for a maximum period of 6 weeks when stored at or below 30 °C. 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.

6.5 Nature and contents of container:

The plastic Ellipta inhaler consists of a light grey body, a light brown mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid.

Each Ellipta inhaler is packed into a carton. The Ellipta inhaler is available in two pack sizes, delivering either 14 or 30 inhalations.

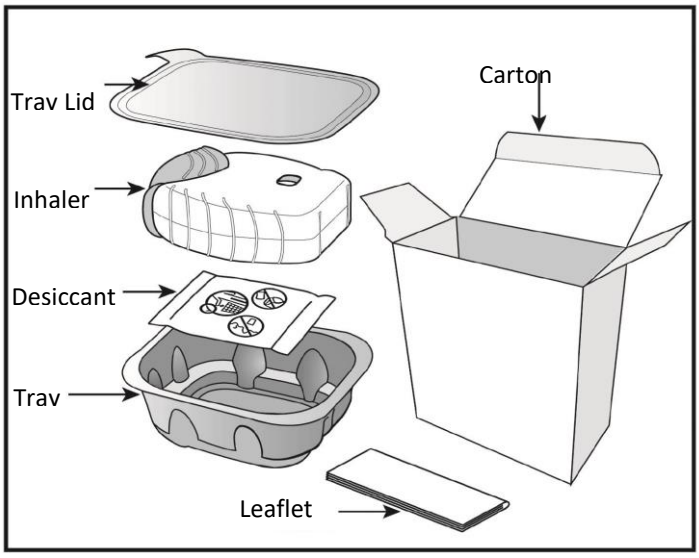
6.6 Special precautions for disposal and/or handling:

No special requirements for disposal.

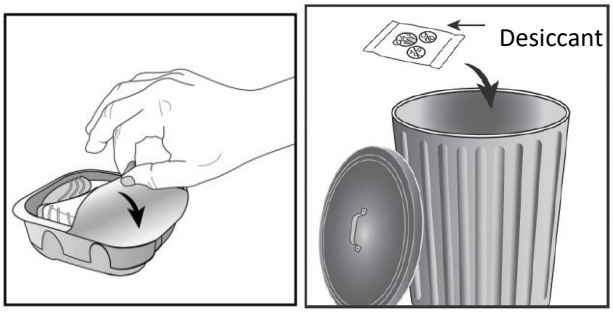
How to use the Ellipta Inhaler:

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 the instructions below.

Your Ellipta inhaler carton contains:



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



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

The "Discard by" date is 6 weeks from the date you open the tray. **After this date, the inhaler should no longer be used.**

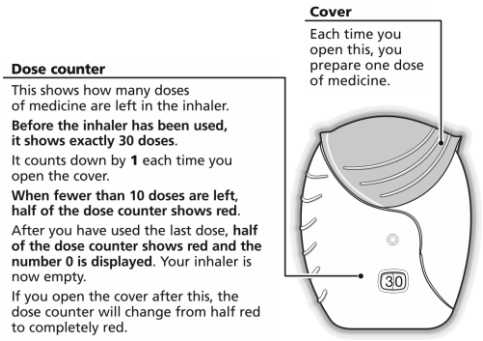
The step-by-step instructions shown below for the 30-dose (30-day supply) Ellipta inhaler also apply to the 14-dose (14-day supply) Ellipta inhaler.

a) Read this before you start:

If you open and close the cover without inhaling the medicine, you will lose the dose.

The lost dose will be securely held inside the inhaler, but it will no longer be available.

It is not possible to accidentally take extra medicine or a double dose in one inhalation.

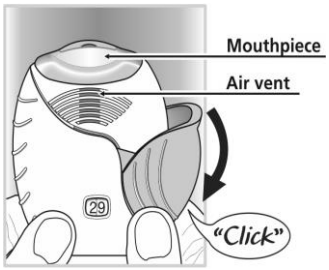


b) Prepare a dose:

Wait to open the cover until you are ready to take your dose.

Do not shake the inhaler.

- Slide the cover fully down until you hear a "click".



Your medicine is now ready to be inhaled.

The dose counter counts down by 1 to confirm.

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

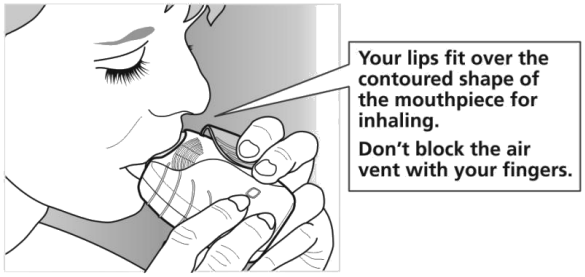
Do not shake the inhaler at any time.

c) Inhale your medication:

While holding the inhaler away from your mouth, breathe out as far as is comfortable. Don’t breathe out into the inhaler.

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

  Don’t block the air vent with your fingers.



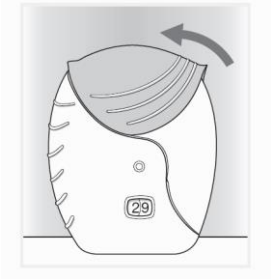
- Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

You may not be able to taste or feel the medicine, even when you are using the inhaler correctly.

If you want to clean the mouthpiece, use a dry tissue, before you close the cover.

d) Close the inhaler and rinse your mouth:

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



- Rinse your mouth with water after you have used the inhaler, do not swallow.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER(S):

TRELEGY Ellipta: 52/21.5.1/0177

9. DATE OF FIRST AUTHORISATION:

01 June 2021

10. DATE OF REVISION OF THE TEXT:

11 April 2024

GDS-12