1. NAME OF THE MEDICINAL PRODUCT

Trelegy Ellipta 100 micrograms/62.5 micrograms/25 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide equivalent to 55 micrograms umeclidinium and 22 micrograms vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate).

Excipient with known effect
Each delivered dose contains approximately 25 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed (inhalation powder).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trelegy Ellipta is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist (for effects on symptom control and prevention of exacerbations see section 5.1).

4.2 Posology and method of administration

Posology

Adults

The recommended and maximum dose is one inhalation of Trelegy Ellipta 92/55/22 micrograms once daily, at the same time each day.

If a dose is missed the next dose should be inhaled at the usual time the next day.

Special populations

Elderly patients

No dose adjustment is required in patients over 65 years (see section 5.2).

Renal impairment

No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild, moderate or severe hepatic impairment. Trelegy Ellipta should be used with caution in patients with moderate to severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

There is no relevant use of Trelegy Ellipta in the paediatric population (under 18 years of age) for the indication of COPD.

Method of administration

Trelegy Ellipta is for inhalation use only.

Instructions for use:

The following instructions for the 30 dose (30 day supply) Ellipta inhaler also apply to the 14 dose (14 day supply) Ellipta inhaler.

a) Prepare a dose

Open the cover when ready to inhale a dose. The inhaler should not be shaken.

Slide the cover down fully until a "click" is heard. The medicinal product is now ready to be inhaled.

The dose counter counts down by 1 to confirm. If the dose counter does not count down as the "click" is heard, the inhaler will not deliver a dose and should be taken back to a pharmacist for advice.

b) How to inhale the medicinal product

The inhaler should be held away from the mouth breathing out as far as is comfortable, but not breathing out into the inhaler.

The mouthpiece should be placed between the lips and the lips should then be closed firmly around it. The air vents should not be blocked with fingers during use.

- Inhale with one long, steady, deep breath in. This breath should be held in for as long as possible (at least 3-4 seconds).
- Remove the inhaler from the mouth.
- Breathe out slowly and gently.

The medicinal product may not be tasted or felt, even when using the inhaler correctly.

The mouthpiece of the inhaler may be cleaned using a dry tissue before closing the cover.

c) 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 to develop a sore mouth or throat as side effects.

For further instructions on handling the device, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Asthma

Trelegy Ellipta should not be used in patients with asthma since it has not been studied in this patient population.

Not for acute use

There are no clinical data to support the use of Trelegy Ellipta for the treatment of acute episodes of bronchospasm, or to treat an acute COPD exacerbation (i.e. as a rescue therapy).

Deterioration of disease

Increasing use of short-acting bronchodilators to relieve symptoms may indicate deterioration of disease control. In the event of deterioration of COPD during treatment with Trelegy Ellipta, a re-evaluation of the patient and of the COPD treatment regimen should be undertaken.

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

Paradoxical bronchospasm

Administration of fluticasone furoate/umeclidinium/vilanterol may produce paradoxical bronchospasm with an immediate wheezing and shortness of breath after dosing and may be life-threatening. Treatment with Trelegy Ellipta should be discontinued immediately if paradoxical bronchospasm occurs. The patient should be 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 and sympathomimetics, including umeclidinium and vilanterol, respectively. Therefore, Trelegy Ellipta should be used with caution in patients with unstable or life-threatening cardiovascular disease.

Patients with hepatic impairment

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

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.

Visual disturbance

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

Coexisting conditions

Trelegy Ellipta should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta$_2$-adrenergic agonists.

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

Anticholinergic activity

Trelegy Ellipta should be used with caution in patients with narrow-angle glaucoma or urinary retention. Patients should be informed about the signs and symptoms of acute narrow-angle glaucoma and should be informed to stop using Trelegy Ellipta and to contact their doctor immediately should any of these signs or symptoms develop.

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Hypokalaemia

Beta$_2$-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

No clinically relevant effects of hypokalaemia were observed in clinical studies with Trelegy Ellipta at the recommended therapeutic dose. Caution should be exercised when Trelegy Ellipta is used with other medicinal products that also have the potential to cause hypokalaemia (see section 4.5).

Hyperglycaemia

Beta$_2$-adrenergic agonists may produce transient hyperglycaemia in some patients. No clinically relevant effects on plasma glucose were observed in clinical studies with fluticasone furoate/umeclidinium/vilanterol at the recommended therapeutic dose. There have been reports of increases in blood glucose levels in diabetic patients treated with fluticasone furoate/umeclidinium/vilanterol and this should be considered when prescribing to patients with a history of diabetes mellitus. Upon initiation of treatment with Trelegy Ellipta, plasma glucose should be monitored more closely in diabetic patients.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

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

Interaction with beta-blockers

Beta$_2$-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 inhibitor

Fluticasone furoate and vilanterol are rapidly cleared by extensive first pass metabolism mediated by enzyme CYP3A4.

Caution is advised when co-administering with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, cobicistat-containing products) as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increased potential for adverse reactions. Co-administration should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid adverse reactions, in which case patients should be monitored for systemic corticosteroid adverse reactions. A repeat dose study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (184/22 micrograms) and ketoconazole (400 milligrams, a strong CYP3A4 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$_2$-agonist related systemic effects on heart rate or blood potassium.

Interaction with CYP2D6 inhibitors/CYP2D6 polymorphism

Umeclidinium is a substrate of cytochrome P450 2D6 (CYP2D6). The steady-state pharmacokinetics of umeclidinium was assessed in healthy volunteers lacking CYP2D6 (poor metabolisers). No effect on umeclidinium AUC or C_{max} was observed at a dose 8-fold higher than the therapeutic dose. An approximately 1.3-fold increase in umeclidinium AUC was observed at 16-fold higher dose with no effect on umeclidinium C_{max}. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when fluticasone furoate/umeclidinium/vilanterol is co-administered with CYP2D6 inhibitors or when administered to patients who are genetically deficient in CYP2D6 activity (poor metabolisers).

Interaction with P-glycoprotein inhibitors

Fluticasone furoate, umeclidinium and vilanterol are substrates of the P-glycoprotein transporter (P-gp). The effect of the moderate P-gp inhibitor verapamil (240 mg once daily) on the steady-state pharmacokinetics of umeclidinium and vilanterol was assessed in healthy volunteers. No effect of verapamil was observed on umeclidinium or vilanterol C_{max}. An approximately 1.4-fold increase in umeclidinium AUC was observed with no effect on vilanterol AUC. Based on the magnitude of these changes, no clinically relevant drug interaction is expected when fluticasone furoate/umeclidinium/vilanterol is co-administered with P-gp inhibitors. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

Other long acting antimuscarinics and long acting beta$_2$- adrenergic agonists

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

Hypokalaemia

Concomitant hypokalaemic treatment with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of $beta_2$-adrenergic agonists, therefore caution should be exercised (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of fluticasone furoate/umeclidinium/vilanterol in pregnant women. Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant (see section 5.3).

Administration of Trelegy Ellipta to pregnant women should only be considered if the expected benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

It is unknown whether fluticasone furoate, umeclidinium, vilanterol or their metabolites are excreted in human milk. However, other corticosteroids, muscarinic antagonists and $beta_2$-adrenergic agonists are detected in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Trelegy Ellipta therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of fluticasone furoate/umeclidinium/vilanterol on human fertility. Animal studies indicate no effects of fluticasone furoate, umeclidinium or vilanterol on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Fluticasone furoate/umeclidinium/vilanterol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions with Trelegy Ellipta were nasopharyngitis (7%), headache (5%) and upper respiratory tract infection (2%).

Tabulated summary of adverse reactions
The safety profile of Trelegy Ellipta is based on three phase III clinical studies.

The first study included safety data from 911 patients with COPD who received fluticasone furoate/umeclidinium/vilanterol 92/55/22 micrograms, once daily, for up to 24 weeks, of whom 210 patients received fluticasone furoate/umeclidinium/vilanterol 92/55/22 micrograms once daily for up to 52 weeks, with an active comparator (study CTT116853, FULFIL).

The second study included safety data from 527 patients with COPD who received fluticasone furoate/umeclidinium/vilanterol (92/55/22 micrograms) and 528 patients with COPD who received fluticasone furoate/vilanterol (92/22 micrograms) + umeclidinium (55 micrograms) once daily for up to 24 weeks (study 200812).

The third study included safety data from 4,151 patients with COPD who received fluticasone furoate/umeclidinium/vilanterol 92/55/22 micrograms once daily for up to 52 weeks, with two active comparators (study CTT116855, IMPACT).

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

Adverse reactions detected during these clinical trials are listed by MedDRA system organ class.

The frequency of adverse reactions is defined using the following convention: 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) and not known (cannot be estimated from available data).

System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Pneumonia Upper respiratory tract infection Bronchitis Pharyngitis Rhinitis Sinusitis Influenza Nasopharyngitis Candidiasis of mouth and throat Urinary tract infection	Common
	Viral respiratory tract infection	Uncommon
Nervous system disorders	Headache	Common
Eye disorders	Vision blurred (see section 4.4)	Not known
Cardiac disorders	Supraventricular tachyarrhythmia Tachycardia Atrial fibrillation	Uncommon
Respiratory, thoracic & mediastinal disorders	Cough Oropharyngeal pain	Common
	Dysphonia	Uncommon
Gastrointestinal disorders	Constipation	Common
	Dry mouth	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia Back pain	Common
	Fractures	Uncommon

Description of selected adverse reactions

Pneumonia

In a total of 1810 patients with advanced COPD (mean post bronchodilatory screening FEV_1 45% of predicted, standard deviation (SD) 13%), 65% of whom had experienced a moderate/severe COPD exacerbation in the year prior to study entry (study CTT116853), there was a higher incidence of pneumonia events reported up to 24 weeks in patients receiving Trelegy Ellipta (20 patients, 2%) than in patients receiving budesonide/formoterol (7 patients, <1%). Pneumonia which required hospitalisation occurred in 1% of patients receiving Trelegy Ellipta and <1% of patients receiving budesonide/formoterol up to 24 weeks. One fatal case of pneumonia was reported in a patient who received Trelegy Ellipta. In the subset of 430 patients treated for up to 52 weeks, the incidence of pneumonia events reported in both Trelegy Ellipta and budesonide/formoterol arms was equal at 2%. The incidence of pneumonia with Trelegy Ellipta is comparable with that observed in the fluticasone furoate/vilanterol (FF/VI) 100/25 arm of FF/VI clinical studies in COPD.

In a 52-week study, with a total of 10,355 patients with COPD and a history of moderate or severe exacerbations within the prior 12 months (mean post-bronchodilator screening FEV1 46% of predicted, SD 15%) (study CTT116855), the incidence of pneumonia was 8% (317 patients) for Trelegy Ellipta (n = 4,151), 7% (292 subjects) for fluticasone furoate/vilanterol (n = 4,134), and 5% (97 subjects) for umeclidinium/vilanterol (n = 2,070). Fatal pneumonia occurred in 12 of 4,151 patients (3.5 per 1,000 patient-years) receiving Trelegy Ellipta, 5 of 4,134 patients (1.7 per 1,000 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (2.9 per 1,000 patient-years) receiving umeclidinium/vilanterol.

To report any side effect(s):

Kingdom of Saudi Arabia

-National Pharmacovigilance centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Ext: 2317-2356-2340
- Reporting Hotline: 19999
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

-GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: saudi.safety@gsk.com
- Website: https://gskpro.com/en-sa/
- P.O. Box 55850, Jeddah 21544, Saudi Arabia

4.9 Overdose

An overdose will likely produce signs, symptoms or adverse effects associated with the individual components' pharmacological actions (e.g. Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, dry mouth, visual accommodation disturbances, tachycardia, arrhythmias, tremor, headache, palpitations, nausea, hyperglycaemia and hypokalaemia).

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 medicinal products should be used with caution in patients with a history of bronchospasm.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Fluticasone furoate/umeclidinium/vilanterol is a combination of inhaled synthetic corticosteroid, long-acting muscarinic receptor antagonist and long-acting beta$_2$-adrenergic agonist (ICS/LAMA/LABA). Following oral inhalation, umeclidinium and vilanterol act locally on airways to produce bronchodilation by separate mechanisms and fluticasone furoate reduces inflammation.

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 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, $beta_2$-adrenergic receptor agonist (LABA). The pharmacologic effects of $beta_2$-adrenergic agonists, 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.

Pharmacodynamic effects

Cardiac electrophysiology
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 umeclidinium/vilanterol (UMEC/VI) did not show clinically relevant effects on QT interval at clinical doses of FF, UMEC and VI.

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

Clinical efficacy and safety

The efficacy of Trelegy Ellipta (92/55/22 micrograms), administered as a once-daily treatment, has been evaluated in patients with a clinical diagnosis of COPD in two, active-controlled studies and in a single, non-inferiority study. All three studies were multicentre, randomised, double-blind studies that required patients to be symptomatic with a COPD Assessment Test (CAT) score ≥10 and on daily maintenance treatment for their COPD for at least three months prior to study entry.

FULFIL (CTT116853) was a 24-week study (N=1,810), with an extension up to 52 weeks in a subset of subjects (n=430), that compared Trelegy Ellipta (92/55/22 micrograms) with budesonide/formoterol 400/12 micrograms (BUD/FOR) administered twice-daily. At screening, the mean post-bronchodilator percent predicted FEV_1 was 45% and 65% of patients reported a history of one or more moderate/severe exacerbation in the past year.

IMPACT (CTT116855) was a 52-week study (N=10,355) that compared Trelegy Ellipta (92/55/22 micrograms) with fluticasone furoate/vilanterol 92/22 micrograms (FF/VI) and umeclidinium/vilanterol 55/22 micrograms (UMEC/VI). At screening, the mean post-bronchodilator percent predicted FEV_1 was 46% and over 99% of patients reported a history of one or more moderate/severe exacerbation in the past year.

At study entry, the most common COPD medications reported in the FULFIL and IMPACT studies were ICS +LABA+LAMA (28%, 34% respectively), ICS+LABA (29%, 26% respectively), LAMA+LABA (10%, 8% respectively) and LAMA (9%, 7% respectively). These patients may have also been taking other COPD medications (e.g. mucolytics or leukotriene receptor antagonists).

Study 200812 was a 24-week, non-inferiority study (N=1,055) that compared Trelegy Ellipta (92/55/22 micrograms) with FF/VI (92/22 micrograms) + UMEC (55 micrograms), co-administered once daily as a multi-inhaler therapy in patients with a history of moderate or severe exacerbations within the prior 12 months.

Lung Function
In FULFIL, bronchodilatory effects with Trelegy Ellipta were evident on the first day of treatment and were maintained over the 24-week treatment period (mean changes from baseline in FEV_1 were 90-222 mL on day 1 and 160-339 mL at week 24). Trelegy Ellipta significantly improved ($p<0.001$) lung function (as defined by mean change from baseline in trough FEV_1 at week 24) (see Table 1) and the improvement was maintained in the subset of patients who continued treatment to week 52.

Table 1. Lung function endpoint in FULFIL

	Trelegy Ellipta (N= 911)	**BUD/FOR (N=899)**	**Treatment difference (95% CI)**
			Comparison with BUD/FOR
Trough FEV_1 (L) at Week 24, LS mean change from baseline (SE)[a]	0.142 (0.0083)	-0.029 (0.0085)	0.171 0.148, 0.194

FEV_1=forced expiratory volume in 1 second; L=litres; LS=least squares; SE= standard error, N=number in the intent-to-treat population; CI= confidence interval, [a] Statistically significant treatment difference for FF/UMEC/VI vs. BUD/FOR also observed at the other assessment timepoints (weeks 2, 4 and 12).

In IMPACT, Trelegy Ellipta significantly improved ($p<0.001$) lung function when compared with FF/VI and UMEC/VI over a 52-week period (See Table 2).

Table 2 – Lung function endpoint in IMPACT

	Trelegy Ellipta (N = 4,151)	**FF/VI (N = 4,134)**	**UMEC/VI (N = 2,070)**	**Treatment difference 95% CI**	
				Comparison Trelegy vs. FF/VI	**Comparison Trelegy vs. UMEC/VI**
Trough FEV_1 (L) at Week 52, LS mean change from baseline (SE) [a]	0.094 (0.004)	-0.003 (0.004)	0.040 (0.006)	0.097 0.085, 0.109	0.054 0.039, 0.069

FEV_1= forced expiratory volume in 1 second; L= litres; LS=least squares; SE= standard error; N= number in the intent-to-treat population; CI= confidence interval; [a] Statistically significant treatment differences for FF/UMEC/VI vs. FF/VI and FF/UMEC/VI vs. UMEC/VI were also observed at the other assessment timepoints (Weeks 4, 16, 28, and 40).

In Study 200812, Trelegy Ellipta was non-inferior compared with FF/VI+UMEC, co-administered in two inhalers, in the improvement from baseline in trough FEV_1 at week 24. The pre-specified non-inferiority margin was 50 mL.

Exacerbations
In IMPACT, over 52 weeks, Trelegy Ellipta significantly reduced ($p<0.001$) the annual rate of moderate/severe exacerbations by 15% (95% CI:10, 20) compared with FF/VI (rate; 0.91 vs 1.07 events per patient year) and by 25% (95% CI: 19, 30) compared with UMEC/VI (rate; 0.91 vs 1.21 events per patient year). In FULFIL, based upon data up to 24 weeks, Trelegy Ellipta significantly reduced ($p=0.002$) the annual rate of moderate/severe exacerbations by 35% (95% CI: 14, 51) compared with BUD/FOR.

In IMPACT, Trelegy Ellipta prolonged the time to first moderate/severe exacerbation and significantly decreased ($p<0.001$) the risk of a moderate/severe exacerbation, as measured by time to first exacerbation, compared with both FF/VI (14.8%; 95% CI: 9.3, 19.9) and UMEC/VI (16.0%; 95% CI: 9.4, 22.1). In FULFIL, Trelegy Ellipta significantly decreased the risk of a moderate/severe exacerbation compared with BUD/FOR over 24 weeks (33%; 95% CI: 12, 48; $p=0.004$).

In IMPACT, treatment with Trelegy Ellipta reduced the annual rate of severe exacerbations (i.e., requiring hospitalisation or resulting in death) by 13% compared with FF/VI (95% CI: -1, 24; $p=0.064$). Treatment with Trelegy Ellipta significantly reduced the annual rate of severe exacerbations by 34% compared with UMEC/VI (95% CI: 22, 44; $p<0.001$).

Health-Related Quality of Life
Trelegy Ellipta significantly improved (p<0.001) Health Related Quality of Life (as measured by the St George's Respiratory Questionnaire [SGRQ] total score) in both FULFIL (week 24) when compared with BUD/FOR (-2.2 units; 95% CI: -3.5, -1.0) and IMPACT (week 52) when compared with FF/VI (-1.8 units; 95% CI: -2.4, -1.1) and UMEC/VI (-1.8 units; 95% CI: -2.6, -1.0).

A higher percentage of patients receiving Trelegy Ellipta responded with a clinically meaningful improvement in SGRQ total score in FULFIL at week 24 compared with BUD/FOR (50% and 41% respectively), odds ratios of response vs. non-response (OR) (1.41; 95% CI: 1.16, 1.70) and in IMPACT at week 52 compared with FF/VI and UMEC/VI (42%, 34% and 34% respectively), OR vs. FF/VI (1.41; 95% CI:1.29, 1.55) and OR vs. UMEC/VI (1.41; 95% CI: 1.26, 1.57); all treatment comparisons were statistically significant (p<0.001).

In FULFIL, the proportion of patients who were CAT responders (defined as 2 units below baseline or lower) at week 24, was significantly higher (p<0.001) for patients treated with Trelegy Ellipta compared with BUD/FOR (53% vs. 45%; OR 1.44; 95% CI: 1.19, 1.75). In IMPACT, the proportion of patients who were CAT responders at week 52 was significantly higher (p<0.001) for patients treated with Trelegy Ellipta (42%) compared with FF/VI (37%; OR 1.24; 95% CI: 1.14, 1.36) and UMEC/VI (36%; OR 1.28; 95% CI: 1.15, 1.43).

Symptom Relief
Breathlessness was measured using the Transition Dyspnoea Index (TDI) focal score at week 24 in FULFIL and week 52 in IMPACT (a subset of patients, n=5,058). In FULFIL the proportion of responders according to TDI (defined as at least 1 unit) was significantly higher (p<0.001) for Trelegy Ellipta compared with BUD/FOR (61% vs 51%; OR 1.61; 95% CI: 1.33, 1.95). In IMPACT, the proportion of responders was also significantly higher (p<0.001) for Trelegy Ellipta (36%) compared with FF/VI (29%; OR 1.36; 95% CI: 1.19, 1.55) and UMEC/VI (30%; OR 1.33; 95% CI: 1.13, 1.57).

In FULFIL, Trelegy Ellipta improved daily symptoms of COPD as assessed by E-RS: COPD total score, compared with BUD/FOR (≥2 unit decrease from baseline). The proportion of responders during weeks 21-24 was significantly higher (p<0.001) for patients treated with Trelegy Ellipta compared with BUD/FOR (47% and 37% respectively; OR 1.59; 95% CI: 1.30, 1.94).

Use of Rescue Medication
In FULFIL, Trelegy Ellipta significantly reduced (p<0.001) the use of rescue medication between weeks 1-24 compared with BUD/FOR (treatment difference: -0.2 occasions per day; 95% CI: -0.3, -0.1).

In IMPACT, Trelegy Ellipta significantly reduced (p<0.001) the use of rescue medication (occasions per day) at each 4-week time period compared with FF/VI and UMEC/VI. At weeks 49-52, the treatment difference was -0.28 (95% CI: -0.37, -0.19) when compared with FF/VI and -0.30 (95% CI: -0.41, -0.19) with UMEC/VI.

Nighttime awakenings
In IMPACT, Trelegy Ellipta statistically significantly reduced the mean number of nighttime awakenings due to COPD compared with FF/VI (-0.05; 95% CI: -0.08, -0.01; p=0.005) and with UMEC/VI (-0.10; 95% CI: -0.14, -0.05; p<0.001) at weeks 49 to 52. Significant reductions were observed over all other timepoints for UMEC/VI (p<0.001) and for the all but two of the of timepoints for FF/VI (p≤0.021).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Trelegy Ellipta in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Population PK analyses for FF/UMEC/VI were conducted using a combined PK dataset from three phase III studies in 821 COPD subjects. Systemic drug levels (steady state C_{max} and AUC) of FF, UMEC and VI following FF/UMEC/VI in one inhaler (triple combination) were within the range of those observed following FF/VI + UMEC as two inhalers, dual combinations (FF/VI and UMEC/VI) as well as individual single inhalers (FF, UMEC and VI). Covariate analysis showed higher FF apparent clearance (42%) when comparing FF/VI to FF/UMEC/VI; however, this is not considered clinically relevant.

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 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 27%, with negligible contribution from oral absorption. Following repeat dosing of inhaled umeclidinium/vilanterol, steady state was achieved within 6 days with up to 1.5-fold accumulation.

Distribution

Fluticasone furoate
Following intravenous dosing of fluticasone furoate to healthy volunteers, the mean volume of distribution at steady state of 661 litres. 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%.

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

Vilanterol
Following intravenous administration of vilanterol to healthy volunteers, the mean volume of distribution at steady state was 165 litres. Vilanterol has a low association with red blood cells. *In vitro* plasma protein binding in human plasma was on average 94%.

Biotransformation

Fluticasone furoate
In vitro studies showed that fluticasone furoate is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic route for fluticasone furoate is 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 primarily metabolised by cytochrome P450 2D6 (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 primarily metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate for the P-gp transporter. The primary metabolic routes for vilanterol are O-dealkylation to a range of metabolites with significantly reduced $beta_1$- and $beta_2$-adrenergic agonist activity. Plasma metabolic profiles following oral administration of vilanterol in a human radiolabel study were consistent with high first-pass metabolism. Systemic exposure to the metabolites is low.

Elimination

Fluticasone furoate
The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of fluticasone furoate/vilanterol was, on average, 24 hours. Following intravenous administration, the elimination phase half-life averaged 15.1 hours. Plasma clearance following intravenous administration was 65.4 litres/hour. Urinary excretion accounted for approximately 2 % of the intravenously administered dose. Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine.

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

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

Special populations

Elderly
The effects of age on the pharmacokinetics of fluticasone furoate, umeclidinium and vilanterol were evaluated in the population pharmacokinetic analysis. No clinically relevant effects requiring dose adjustment were observed.

Renal impairment
The effect of 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 that showed no evidence of an increase in systemic exposure to fluticasone furoate, umeclidinium or vilanterol. *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
The effect of 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.

The fluticasone furoate/vilanterol component of Trelegy Ellipta was assessed in patients with all severities of hepatic impairment (Child-Pugh A, B or C). For fluticasone furoate, patients with moderate hepatic impairment showed up to three times higher systemic exposure (FF 184 micrograms); therefore, patients with severe hepatic impairment received half the dose (FF 92 micrograms). At this dose, no effects on systemic exposure were observed. Therefore caution is advised in moderate to severe hepatic impairment, but no specific dose adjustment based on hepatic function is recommended. There was no significant increase in systemic exposure to vilanterol.

Patients with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC). Umeclidinium has not been evaluated in patients with severe hepatic impairment.

Other special populations
The effects of race, gender and weight on the pharmacokinetics of fluticasone furoate, umeclidinium and vilanterol were also evaluated in the population pharmacokinetic analysis.

In 113 East Asian subjects with COPD (Japanese and East Asian Heritage), who received FF/UMEC/VI from a single inhaler (27% subjects), fluticasone furoate $AUC_{(ss)}$ estimates were on average 30% higher compared with Caucasian subjects. However, these higher systemic exposures remain below the threshold for FF-induced reduction of serum and urine cortisol and are not considered clinically relevant. There was no effect of race on pharmacokinetic parameters of umeclidinium or vilanterol in subjects with COPD.

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

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

Pharmacological and toxicological effects seen with fluticasone furoate, umeclidinium or vilanterol in nonclinical studies were those typically associated with glucocorticoids, muscarinic receptor antagonists, or $beta_2$-adrenergic receptor agonists. Administration of combined fluticasone furoate, umeclidinium and vilanterol to dogs did not result in any significant new toxicity or any major exacerbation of expected findings associated with fluticasone furoate, umeclidinium or vilanterol alone.

Genotoxicity and carcinogenicity

Fluticasone furoate
Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures of 1.4- or 2.9-fold, respectively, those seen in humans at a daily dose of 92 micrograms fluticasone furoate, based on AUC.

Umeclidinium
Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 20- or ≥ 17- fold the human clinical exposure at a daily dose of 55 micrograms umeclidinium, based on AUC respectively.

Vilanterol
Vilanterol (as alpha-phenylcinnamate) and triphenylacetic acid were not genotoxic indicating that vilanterol (as trifenatate) does not represent a genotoxic hazard to humans. Consistent with findings for other $beta_2$ agonists, in lifetime inhalation studies vilanterol trifenatate caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice

at exposures 0.9- or 22-fold, respectively, the human clinical exposure of vilanterol at a daily dose of 22 micrograms based on AUC.

Toxicity to reproduction

Fluticasone furoate, umeclidinium and vilanterol did not have any adverse effects on male or female fertility in rats.

Fluticasone furoate
Fluticasone furoate was not teratogenic in rats or rabbits, but delayed development in rats and caused abortion in rabbits at maternally toxic doses. There were no effects on development in rats at exposures 6.6-fold the human clinical exposure at a daily dose of 92 micrograms, based on AUC. Fluticasone furoate had no adverse effect on pre- or post-natal development in rats.

Umeclidinium
Umeclidinium was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium to rats resulted in lower maternal body weight gain and food consumption and slightly decreased pre-weaning pup body weights in dams given 180 micrograms/kg/day dose (approximately 61-fold the human clinical exposure of umeclidinium at a daily dose of 55 micrograms, based on AUC).

Vilanterol
Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, vilanterol caused effects similar to those seen with other beta$_2$-adrenergic agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 62-fold the human clinical exposure at a daily dose of 22 micrograms, based on AUC. Vilanterol had no adverse effect on pre- or post-natal development in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date is indicated on the packaging.

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

6.4 Special precautions for storage

Do not store above 30°C.
If stored in a refrigerator allow the inhaler to return to room temperature for at least an hour before use.

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

Write the date that the inhaler should be discarded on the label and carton 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 Ellipta inhaler consists of a light grey body, beige mouthpiece cover and a dose counter, packed into a foil laminate tray containing a silica gel desiccant sachet. The tray is sealed with a peelable foil lid.

The inhaler is a multi-component device composed of polypropylene, high density polyethylene, polyoxymethylene, polybutylene terephthalate, acrylonitrile butadiene styrene, polycarbonate and stainless steel.

The inhaler contains two aluminium foil laminate blister strips that deliver a total of 14 or 30 doses (14 or 30 day supply). Each blister in one strip contains fluticasone furoate, each blister in the other strip contains umeclidinium (as bromide) and vilanterol (as trifenatate).

Pack sizes of 14 or 30 dose inhalers.
Multipack of 90 (3 packs of 30) dose inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

The Ellipta inhaler contains pre-dispensed doses and is ready to use.

The inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. The desiccant sachet should be thrown away and it should not be opened, eaten or inhaled. The patient should be advised to not open the tray until they are ready to inhale a dose.

The inhaler will be in the 'closed' position when it is first taken out of its sealed tray. The "Discard by" date should be written on the inhaler label and carton in the space provided. The date should be added as soon as the inhaler has been removed from the tray. The "Discard by" date is 6 weeks from the date of opening the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

If the inhaler cover is opened and closed without inhaling the medicinal product, the dose will be lost. The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.

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

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

7. MARKETING AUTHORISATION HOLDER

Glaxo Saudi Arabia Ltd* , PO Box 22617, Area No 56 to 73
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Saudi Arabia

8. MANUFACTURER

Glaxo Operations UK Ltd*, Ware, hertfordshire, United Kingdom.
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