Relvar Ellipta 92/22 mcg
Relvar Ellipta 184/22 mcg

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 92/22 mcg.

Relvar Ellipta 184/22 mcg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Relvar Ellipta 92/22 mcg: Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 100 micrograms of fluticasone furoate and 25 micrograms vilanterol (as trifenatate).

Relvar Ellipta 184/22 mcg: Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 200 micrograms of fluticasone furoate and 25 micrograms vilanterol (as trifenatate).

Excipient with known effect

Each delivered dose contains approximately 25 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma
Relvar Ellipta 92/22 mcg and Relvar Ellipta 184/22 mcg is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting $beta_2$-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting $beta_2$-agonists.
- patients already adequately controlled on both inhaled corticosteroid and long-acting $beta_2$-agonist.

COPD (Chronic Obstructive Pulmonary Disease)

Relvar Ellipta 92/22 mcg is indicated for the symptomatic treatment of adults with COPD with a FEV_1<70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

4.2 Posology and method of administration

Posology

Asthma

Patients with asthma should be given the strength of Relvar Ellipta containing the appropriate fluticasone furoate (FF) dosage for the severity of their disease. Prescribers should be aware that in patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily, while FF 200 micrograms once daily is approximately equivalent to FP 500 micrograms twice daily.

Adults and adolescents aged 12 years and over

A starting dose of one inhalation of Relvar Ellipta 92/22 micrograms once daily should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.

Patients should be regularly reassessed by a healthcare professional so that the strength of fluticasone furoate/vilanterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Relvar Ellipta 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting beta$_2$-agonist.

Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic.

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

The maximum recommended dose is Relvar Ellipta 184/22 micrograms once daily.

Children aged under 12 years

The safety and efficacy of Relvar Ellipta in children under 12 years of age have not been established in the indication for asthma.
Relvar Ellipta should not be used in children under 12 years of age. Currently available data are described in sections 5.1 and 5.2.

COPD

Adults aged 18 years and over

One inhalation of Relvar Ellipta 92/22 micrograms once daily.

Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions (see sections 4.4 and 4.8).

Patients usually experience an improvement in lung function within 16-17 minutes of inhaling Relvar Ellipta.

Paediatric population

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

Special populations

Elderly

No dose adjustment is required in patients 65 years of age or older (see section 5.2).

Renal impairment

No dose adjustment is required in this population (see section 5.2).
Hepatic impairment

Studies in subjects with mild, moderate and severe hepatic impairment showed an increase in systemic exposure to fluticasone furoate (both C_{max} and AUC) (see section 5.2).
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 92/22 micrograms (see section 4.4).

Method of administration

Relvar Ellipta is for oral inhalation only.

It should be administered at the same time of the day, each day.

The final decision on evening or morning dosing should be left to the discretion of the physician.

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

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

If stored in a refrigerator, the inhaler should be allowed to return to room temperature for at least an hour before use.

When the inhaler is used for the first time, there is no need to check that it is working properly, and to prepare it for use in any special way. The step-by-step instructions should be followed.

The Ellipta 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.

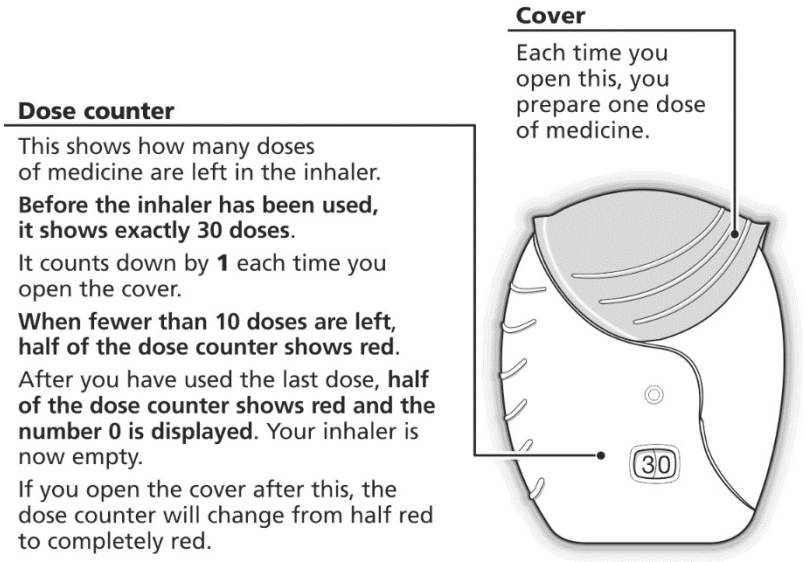
When the inhaler is taken out of its tray, it will be in the ‘closed’ position. The “Discard by” date should be written on the inhaler label and carton in the space provided. The “Discard by” date is 6 weeks from the date of opening the tray, but not later than the expiry date. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

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

Instructions for use

1. Read this before you start

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 medicinal product or a double dose in one inhalation.

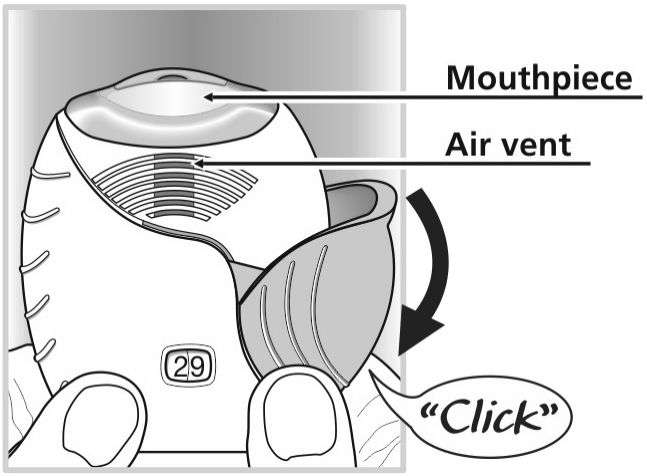


2. Prepare a dose

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

Slide the cover down 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.



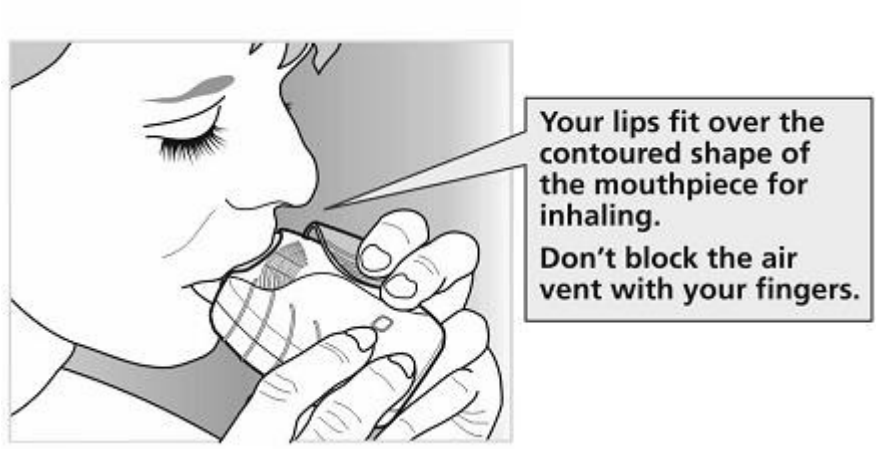
3. How to inhale the medicinal product

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 lips and the lips should be then closed firmly around it.

The air vents should not be blocked with fingers during use.

- Inhale with one long, steady, deep breath in. The breath should be held 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.

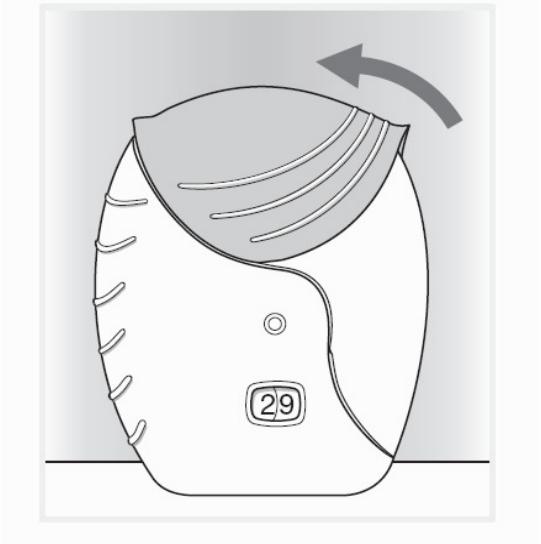
The mouthpiece of the inhaler may be cleaned using a **dry tissue before** closing the cover.

4. 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.



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

Deterioration of disease

Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms or an acute exacerbation in COPD, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop therapy with fluticasone furoate/vilanterol in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

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

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. Relvar Ellipta should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including Relvar Ellipta. In a placebo-controlled study in subjects with moderate COPD and a history of, or an increased risk of cardiovascular disease, there was no increase in the risk of cardiovascular events in patients receiving fluticasone furoate/vilanterol compared with placebo (see section 5.1). However, fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Patients with hepatic impairment

For patients with moderate to severe hepatic impairment, the 92/22 micrograms dose should be used and patients 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. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Fluticasone furoate/vilanterol should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

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.

Hyperglycaemia

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

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.

Pneumonia in patients with asthma

The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the 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/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. Concurrent use of both non-selective and selective beta$_2$-adrenergic 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 liver enzyme CYP3A4.

Caution is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir, cobicistat-containing products) as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol. Co-administration should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid undesirable effects, in which case patients should be monitored for systemic corticosteroid undesirable effects. A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (184/22 micrograms) and the strong CYP3A4 inhibitor ketoconazole (400 mg). 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} 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, blood potassium or QTcF interval

Interaction with P-glycoprotein inhibitors

Fluticasone furoate and vilanterol are both substrates of P-glycoprotein (P-gp). A clinical pharmacology study in healthy subjects with co-administered vilanterol and the potent P-gp and moderate CYP3A4 inhibitor verapamil did not show any significant effect on the pharmacokinetics of vilanterol. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

Sympathomimetic medicinal products

Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) may potentiate the adverse reactions of fluticasone furoate/vilanterol. Relvar Ellipta should not be used in conjunction with other long-acting beta$_2$-adrenergic agonists or medicinal products containing long-acting beta$_2$-adrenergic agonists.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant (see section 5.3). There are no or limited data from the use of fluticasone furoate and vilanterol trifenatate in pregnant women.

Administration of fluticasone furoate/vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding

There is insufficient information on the excretion of fluticasone furoate or vilanterol trifenatate and/or metabolites in human milk. However, other corticosteroids and beta$_2$-agonists are detected in human milk (see section 5.3). A risk to breastfed newborns/infants cannot be excluded.

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

Fertility

There are no fertility data in humans. Animal studies showed no effect of fluticasone furoate/vilanterol trifenatate on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with fluticasone furoate/vilanterol. In the asthma clinical development programme a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development programme a total of 6,237 subjects were included in an integrated assessment of adverse reactions.

The most commonly reported adverse reactions with fluticasone furoate and vilanterol were headache and nasopharyngitis. With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently observed in patients with COPD.

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class and frequency. The following convention has been used for the classification of frequencies: 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).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Pneumonia* Upper respiratory tract infection Bronchitis Influenza Candidiasis of mouth and throat	Common
Immune system disorders	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria.	Rare
Metabolism and nutrition disorders	Hyperglycaemia	Uncommon
Psychiatric disorders	Anxiety	Rare
Nervous system disorders	Headache Tremor	Very common Rare
Eye disorders	Vision blurred (see section 4.4)	Uncommon
Cardiac disorders	Extrasystoles Palpitations Tachycardia	Uncommon Rare Rare
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis Oropharyngeal pain Sinusitis Pharyngitis Rhinitis Cough Dysphonia Paradoxical bronchospasm	Very common Common Rare
Gastrointestinal disorders	Abdominal pain	Common
Musculoskeletal and connective tissue disorders	Arthralgia Back pain Fractures** Muscle spasms	Common
General disorders and administration site conditions	Pyrexia	Common

*, ** See below 'Description of selected adverse reactions'

Description of selected adverse reactions
**Pneumonia* (see section 4.4)

In an integrated analysis of the two replicate one year studies in moderate to severe COPD (mean predicted post-bronchodilator screening FEV_1 of 45%, standard deviation (SD) 13%) with an exacerbation in the preceding year (n = 3255), the number of pneumonia events per 1000 patient years was 97.9 with FF/VI

184/22 micrograms, 85.7 in the FF/VI 92/22 micrograms and 42.3 in the VI 22 micrograms group. For severe pneumonia the corresponding number of events per 1000 patient years were 33.6, 35.5, and 7.6 respectively, while for serious pneumonia the corresponding events per 1000 patient years were 35.1 for FF/VI 184/22 micrograms, 42.9 with FF/VI 92/22 micrograms, 12.1 with VI 22 micrograms. Finally, the exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 184/22 micrograms versus 1.5 for FF/VI 92/22 micrograms and 0 for VI 22 micrograms.

In a placebo-controlled study (SUMMIT) in subjects with moderate COPD (mean percent post-bronchodilator screening FEV_1 of 60%, SD 6%), and a history of, or an increased risk of cardiovascular disease, the incidence of pneumonia with FF/VI, FF, VI and placebo was: adverse events (6%, 5%, 4%, 5%); serious adverse events (3%, 4%, 3%, 3%); adjudicated on treatment deaths due to pneumonia (0.3%, 0.2%, 0.1%, 0.2%); the exposure adjusted rates (per 1000 treatment years) were: adverse events (39.5, 42.4, 27.7, 38.4); serious adverse events (22.4, 25.1, 16.4, 22.2); adjudicated on-treatment deaths due to pneumonia (1.8, 1.5, 0.9, 1.4) respectively.

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia per 1000 patient years was 18.4 for FF/VI 184/22 micrograms versus 9.6 for FF/VI 92/22 micrograms and 8.0 in the placebo group.

***Fractures*

In two replicate 12 month studies in a total of 3,255 patients with COPD the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all Relvar Ellipta groups (2%) compared with the vilanterol 22 micrograms group (<1%). Although there were more fractures in the Relvar Ellipta groups compared with the vilanterol 22 micrograms group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the Relvar Ellipta and vilanterol treatment arms.

For the SUMMIT study, the incidence of all events of fracture with FF/VI, FF, VI and placebo were 2% in each arm; fractures commonly associated with ICS use were less than 1 % in each arm. The exposure-adjusted rates (per 1000 treatment years) for all fracture events were 13.6, 12.8, 13.2, 11.5 respectively; fractures commonly associated with ICS use were 3.4, 3.9, 2.4, 2.1 respectively.

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures was <1%, and usually associated with trauma.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.
Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

Symptoms and signs

An overdose of fluticasone furoate/vilanterol may produce signs and symptoms due to the individual component's actions, including those seen with overdose of other $beta_2$-agonists and consistent with the known inhaled corticosteroid class effects (see section 4.4).

Treatment

There is no specific treatment for an overdose with fluticasone furoate/vilanterol. 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 as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics ATC code: R03AK10.

Mechanism of action

Fluticasone furoate and vilanterol represent two classes of medications (a synthetic corticosteroid and a selective, long-acting beta$_2$-receptor agonist).

Pharmacodynamic effects

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).

Vilanterol trifenatate

Vilanterol trifenatate is a selective long-acting, beta$_2$-adrenergic agonist (LABA).
The pharmacologic effects of beta$_2$-adrenoceptor agonist active substances, including vilanterol trifenatate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the beta$_2$-receptor gene, increasing receptor number and sensitivity and LABAs prime the glucocorticoid receptor for steroid-dependent activation and enhance cell nuclear translocation. These synergistic interactions are reflected in enhanced anti-inflammatory activity, which has been demonstrated *in vitro* and *in vivo* in a range of inflammatory cells relevant to the pathophysiology of both asthma and COPD. In peripheral blood mononuclear cells from subjects with COPD, a larger anti-inflammatory effect was seen in the presence of the combination of fluticasone furoate/vilanterol compared with fluticasone furoate alone at concentrations achieved with clinical doses. The enhanced anti-inflammatory effect of the LABA component was similar to that obtained with other ICS/LABA combinations.

Clinical efficacy and safety

Asthma

Three phase III randomised, double-blind studies (HZA106827, HZA106829 and HZA106837) of different durations evaluated the safety and efficacy of fluticasone furoate/vilanterol in adult and adolescent patients with persistent asthma. All subjects were using an ICS (Inhaled corticosteroid) with or without LABA for at

least 12 weeks prior to visit 1. In HZA106837 all patients had at least one exacerbation that required treatment with oral corticosteroids in the year prior to visit 1. HZA106827 was 12 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 92/22 micrograms [n=201] and FF 92 micrograms [n=205]) compared with placebo [n=203], all administered once daily. HZA106829 was 24 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 184/22 micrograms [n=197] and FF 184 micrograms [n=194]) both administered once daily compared with FP 500 micrograms twice daily [n=195].

In HZA106827/HZA106829 the co-primary efficacy endpoints were change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the treatment period in all subjects and weighted mean serial FEV_1 over 0-24 hours post-dose calculated in a subset of subjects at the end of the treatment period. Change from baseline in the percentage of rescue-free 24 hour periods during treatment was a powered secondary endpoint. Results for the primary and key secondary endpoints in these studies are described in Table 1.

Table 1 - Results of primary and key secondary endpoints in HZA106827 and HZA106829

Study No.	**HZA106829**		**HZA106827**	
Treatment Dose of FF/VI*(micrograms)	FF/VI 184/22 Once Daily vs FF 184 Once Daily	FF/VI 184/22 Once Daily vs FP 500 Twice Daily	FF/VI 92/22 Once Daily vs FF 92 Once Daily	FF/VI 92/22 Once Daily vs placebo Once Daily
Change from Baseline in Trough FEV_1 Last Observation Carried Forward (LOCF)				
Treatment difference	193 mL	210 mL	36 mL	172 mL
P value	p<0.001	p<0.001	p=0.405	p<0.001
(95% CI)	(108, 277)	(127, 294)	(-48, 120)	(87, 258)
Weighted Mean Serial FEV_1 over 0-24 hours post-dose				
Treatment difference	136 mL	206 mL	116 mL	302 mL
P value	p=0.048	p=0.003	p=0.06	p<0.001
(95% CI)	(1, 270)	(73, 339)	(-5, 236)	(178, 426)
Change from Baseline in Percentage of Rescue-Free 24-hour Periods				
Treatment difference	11.7%	6.3%	10.6%	19.3%
P value	p<0.001	p=0.067	p<0.001	p<0.001
(95% CI)	(4.9, 18.4)	(-0.4, 13.1)	(4.3, 16.8)	(13.0, 25.6)
Change from Baseline in Percentage of Symptom-Free 24-hour Periods				
Treatment difference	8.4%	4.9%	12.1%	18.0%
P value	p=0.010	p=0.137	p<0.001	p<0.001
(95% CI)	(2.0, 14.8)	(-1.6, 11.3)	(6.2, 18.1)	(12.0, 23.9)
Change from Baseline in AM Peak Expiratory Flow				
Treatment difference	33.5 L/min	32.9 L/min	14.6 L/min	33.3 L/min
P value	p<0.001	p<0.001	p<0.001	p<0.001
(95% CI)	(22.3, 41.7)	(24.8, 41.1)	(7.9, 21.3)	(26.5, 40.0)
Change from Baseline in PM Peak Expiratory Flow				
Treatment difference	30.7 L/min	26.2 L/min	12.3 L/min	28.2 L/min
P value	p<0.001	p<0.001	p<0.001	p<0.001
(95% CI)	(22.5, 38.9)	(18.0, 34.3)	(5.8, 18.8)	(21.7, 34.8)

**FF/VI = fluticasone furoate/vilanterol*

HZA106837 was of variable treatment duration (from a minimum of 24 weeks to a maximum of 76 weeks with the majority of patients treated for at least 52 weeks). In HZA106837 patients were randomised to receive either fluticasone furoate/vilanterol 92/22 micrograms [n=1009] or FF 92 micrograms [n=1010] both administered once daily. In HZA106837 the primary endpoint was the time to first severe asthma exacerbation. A severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Adjusted mean change from baseline in trough FEV_1 was also evaluated as a secondary endpoint.

In HZA106837 the risk of experiencing a severe asthma exacerbation in patients receiving fluticasone furoate/vilanterol 92/22 micrograms was reduced by 20% compared with FF 92 micrograms alone (hazard ratio 0.795, p=0.036 95% CI 0.642, 0.985). The rate of severe asthma exacerbations per patient per year was 0.19 in the FF 92 micrograms group (approximately 1 in every 5 years) and 0.14 in the fluticasone furoate/vilanterol 92/22 micrograms group (approximately 1 in every 7 years). The ratio of the exacerbation rate for fluticasone furoate/vilanterol 92/22 micrograms versus FF 92 micrograms was 0.755 (95% CI 0.603, 0.945). This represents a 25% reduction in the rate of severe asthma exacerbations for subjects treated with fluticasone furoate/vilanterol 92/22 micrograms compared with FF 92 micrograms(p=0.014). The 24-hour bronchodilator effect of fluticasone furoate/vilanterol was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). Fluticasone furoate/vilanterol 92/22 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV_1 at weeks 12, 36 and 52 and Endpoint compared with FF 92 micrograms (p<0.001 95% CI 52, 126 mL at Endpoint). Forty four percent of patients in the fluticasone furoate/vilanterol 92/22 micrograms group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 92 micrograms group (p<0.001 95% CI 1.23, 1.82).

Studies versus salmeterol/fluticasone propionate combinations

In a 24 week study (HZA113091) in adult and adolescent patients with uncontrolled persistent asthma both fluticasone furoate/vilanterol 92/22 micrograms given once daily in the evening and salmeterol/FP 50/250 micrograms given twice daily demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV_1 of 341 mL (fluticasone furoate/vilanterol) and 377 mL (salmeterol/FP) demonstrated an overall improvement in lung function over 24 hours for both treatments. The adjusted mean treatment difference of 37 mL between the groups was not statistically significant (p=0.162). For trough FEV_1 subjects in the fluticasone furoate/vilanterol group achieved a LS mean change from baseline of 281 mL and subjects in the salmeterol/FP group a change of 300 mL; (the difference in adjusted mean of 19 mL (95%CI:-0.073, 0.034) was not statistically significant (p=0.485).

A randomised, double-blind, parallel group, 24 week study (201378) was conducted to demonstrate non-inferiority (using a margin of -100 mL for trough FEV_1) of fluticasone furoate/vilanterol 92/22 micrograms once daily to salmeterol/FP 50/250 micrograms twice daily in adults and adolescents whose asthma was well controlled following 4 weeks of treatment with open-label salmeterol/FP 50/250 micrograms twice daily (N=1504). Subjects randomised to once-daily FF/VI maintained lung function comparable with those randomised to twice-daily salmeterol/FP [difference in trough FEV_1 of +19 mL (95% CI: -11, 49)].

No comparative studies versus salmeterol/FP or versus other ICS/LABA combinations have been conducted to appropriately compare the effects on asthma exacerbations.

Fluticasone furoate monotherapy

A 24 week randomised, double-blind placebo controlled study (FFA112059) evaluated the safety and efficacy of FF 92 micrograms once daily [n= 114] and FP 250 micrograms twice daily [n=114] versus placebo [n=115] in adult and adolescent patients with persistent asthma. All subjects had to have been on a stable dose of an ICS for at least 4 weeks prior to visit 1 (screening visit) and the use of LABAs was not permitted within 4 weeks of visit 1. The primary efficacy endpoint was change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1 at the end of the treatment period. Change from baseline in the percentage of rescue-free 24-hour periods during the 24-week treatment period was a powered secondary. At the 24-week time point FF and FP increased trough FEV_1 by 146 mL (95% CI 36, 257 mL, p=0.009) and 145 mL (95% CI 33, 257 mL, p=0.011) respectively compared to placebo. FF and FP both increased the percentage of 24-hour rescue-free periods by 14.8% (95% CI 6.9, 22.7, p<0.001) and 17.9% (95% CI 10.0, 25.7, p<0.001) respectively versus placebo.

Allergen challenge study

The bronchoprotective effect of fluticasone furoate/vilanterol 92/22 micrograms on the early and late asthmatic response to inhaled allergen was evaluated in a repeat dose, placebo-controlled four-way crossover study (HZA113126) in patients with mild asthma. Patients were randomized to receive fluticasone furoate/vilanterol 92/22 micrograms, FF 92 micrograms, vilanterol 22 micrograms or placebo once daily for 21 days followed by challenge with allergen 1 hour after the final dose. The allergen was house dust mite, cat dander, or birch pollen; the selection was based on individual screening tests. Serial FEV_1 measurements were compared with pre-allergen challenge values taken after saline inhalation (baseline). Overall, the greatest effects on the early asthmatic response were seen with fluticasone furoate/vilanterol 92/22 micrograms compared with FF 92 micrograms or vilanterol 22 micrograms alone. Both fluticasone furoate/vilanterol 92/22 micrograms and FF 92 micrograms virtually abolished the late asthmatic response compared with vilanterol alone. Fluticasone furoate/vilanterol 92/22 micrograms provided significantly greater protection against allergen-induced bronchial hyper-reactivity compared with monotherapies FF and vilanterol as assessed on Day 22 by methacholine challenge.

Bronchoprotective and HPA-axis effects study

The bronchoprotective and HPA-axis effects of FF versus FP or budesonide (BUD) were evaluated in an escalating repeat-dose, placebo-controlled, crossover study (203162) in 54 adults with a history of asthma, characterised by airway hyperresponsiveness and FEV_1 ≥65% predicted. Patients were randomised to one or two treatment periods, comprising five 7-day dose-escalation phases of FF (25, 100, 200, 400, 800 micrograms/day), FP (50, 200, 500, 1,000, 2,000 micrograms/day), BUD (100, 400, 800, 1,600, 3,200 micrograms/day), or placebo. After each dose-escalation phase, bronchoprotection via airway hyperresponsiveness to adenosine-5'-monophosphate (AMP) challenge (provocative concentration causing ≥20% decline in FEV_1 [AMP PC20]) and 24-hour weighted mean plasma cortisol were assessed.

Across the approved therapeutic dose ranges for asthma the AMP PC20 (mg/mL) and cortisol suppression (%) values were: 81 to 116 mg/mL and 7% to 14% for FF (100 to 200 micrograms/day), 20 to 76 mg/mL and 7% to 50% for FP (200 to 2,000 micrograms/day), and 24 to 54 mg/mL and 13% to 44% for BUD (400 to 1,600 micrograms/day), respectively.

Chronic Obstructive Pulmonary Disease

The COPD clinical development programme included a 12-week (HZC113107), two 6-month (HZC112206, HZC112207), two one-year (HZC102970, HZC102871), and one >1 year study (SUMMIT). These were randomised controlled studies in patients with a clinical diagnosis of COPD. These studies included measures of lung function, dyspnoea and moderate and severe exacerbations.

Six month studies

HZC112206 and HZC112207 were 24 week randomised, double-blind, placebo controlled, parallel group studies comparing the effect of the combination to vilanterol and FF alone and placebo. HZC112206 evaluated the efficacy of fluticasone furoate/vilanterol 46 /22 micrograms [n=206] and fluticasone furoate/vilanterol 92/22 micrograms [n=206] compared with FF 92 micrograms [n=206], vilanterol 22 micrograms [n=205] and placebo [n = 207], all administered once daily. HZC112207 evaluated the efficacy of fluticasone furoate/vilanterol 92/22 micrograms [n=204] and fluticasone furoate/vilanterol 184/22 micrograms [n=205] compared with FF 92 micrograms [n=204], FF 184 micrograms [n=203] and vilanterol 22 micrograms [n=203] and placebo [n = 205], all administered once daily.

All patients were required to have a smoking history of at least 10 pack years; a post-salbutamol FEV_1/FVC ratio less than or equal to 0.70; post-salbutamol FEV_1 less than or equal to 70% predicted and have a Modified Medical Research Council (mMRC) dyspnea score ≥2 (scale 0-4) at screening. At screening, the mean pre-bronchodilator FEV_1 was 42.6% and 43.6% predicted, and the mean reversibility was 15.9% and 12.0% in HZC112206 and HZC112207, respectively. The co-primary endpoints in both studies were weighted mean FEV_1 from zero to 4 hours post-dose at Day 168 and change from baseline in pre-dose trough FEV_1 at Day 169.

In an integrated analysis of both studies, fluticasone furoate/vilanterol 92/22 micrograms showed clinically meaningful improvements in lung function. At Day 169 fluticasone furoate/vilanterol 92/22 micrograms and vilanterol increased adjusted mean trough FEV_1 by 129 mL (95% CI: 91, 167 mL, p<0.001) and 83 mL (95% CI: 46, 121 mL, p<0.001) respectively compared to placebo. Fluticasone furoate/vilanterol 92/22 micrograms increased trough FEV_1 by 46 mL compared to vilanterol (95% CI: 8, 83 mL, p= 0.017). At Day 168 fluticasone furoate/vilanterol 92/22 micrograms and vilanterol increased adjusted mean weighted mean FEV_1 over 0-4 hours by 193 mL (95% CI: 156, 230 mL, p<0.001) and 145 mL (95% CI: 108, 181 mL, p<0.001) respectively compared to placebo. Fluticasone furoate/vilanterol 92/22 micrograms increased adjusted mean weighted mean FEV_1 over 0-4 hours by 148 mL compared to FF alone (95% CI: 112, 184 mL, p< 0.001).

12 month studies

Studies HZC102970 and HZC102871 were 52 week randomised, double-blind, parallel-group, studies comparing the effect of fluticasone furoate/vilanterol 184/22 micrograms, fluticasone furoate/vilanterol 92/22 micrograms, fluticasone furoate/vilanterol 46/22 micrograms with vilanterol 22 micrograms, all administered once daily, on the annual rate of moderate/severe exacerbations in subjects with COPD with a smoking history of at least 10 pack years and a post-salbutamol FEV_1/FVC ratio less than or equal to 0.70 and post-salbutamol FEV_1 less than or equal to 70% predicted and documented history of ≥ 1 COPD exacerbation that required antibiotics and/or oral corticosteroids or hospitalisation in the 12 months prior to visit 1. The primary endpoint was the annual rate of moderate and severe exacerbations. Moderate/ severe exacerbations were defined as worsening symptoms that required treatment with oral corticosteroids and/or antibiotics or in-patient hospitalisation. Both studies had a 4 week run-in period during which all subjects received open-label salmeterol/FP 50/250 micrograms twice daily to standardise COPD pharmacotherapy and stabilise disease prior to randomisation to blinded study medication for 52 weeks. Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting bronchodilators ($beta_2$-agonist and anticholinergic), ipratropium/salbutamol combination products, oral $beta_2$-agonists, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of both studies showed that treatment with fluticasone furoate/vilanterol 92/22 micrograms once daily resulted in a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol (Table 2).

Table 2: Analysis of Exacerbation Rates following 12 months of treatment

Endpoint	HZC102970		HZC102871		HZC102970 and HZC102871 integrated	
	Vilanterol (n=409)	fluticasone furoate/ vilanterol 92/22 (n=403)	Vilanterol (n=409)	fluticasone furoate/ vilanterol 92/22 (n=403)	Vilanterol (n=818)	fluticasone furoate/ vilanterol 92/22 (n=806)
Moderate and severe exacerbations						
Adjusted mean annual rate	1.14	0.90	1.05	0.70	1.11	0.81
Ratio vs VI 95% CI p-value % reduction (95% CI)		0.79 (0.64,0.97) 0.024 21 (3, 36)		0.66 (0.54, 0.81) <0.001 34 (19, 46)		0.73 (0.63, 0.84) <0.001 27 (16, 37)
Absolute difference in number per year vs VI (95% CI)		0.24 (0.03, 0.41)		0.36 (0.20, 0.48)		0.30 (0.18, 0.41)
Time to first exacerbation: Hazard ratio (95% CI) % risk reduction p-value		0.80 (0.66, 0.99) 20 0.036		0.72 (0.59, 0.89) 28 0.002		0.76 (0.66, 0.88) 24 p<0.001

In an integrated analysis of HZC102970 and HZC102871 at Week 52, an improvement was seen when comparing the fluticasone furoate/vilanterol 92/22 micrograms versus vilanterol 22 micrograms in adjusted mean trough FEV_1 (42 mL 95% CI: 19, 64 mL, p<0.001). The 24-hour bronchodilator effect of fluticasone furoate/vilanterol was maintained from the first dose throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis).

Overall, across the two studies combined 2009 (62%) patients had cardiovascular history/risk factors at screening. The incidence of cardiovascular history/risk factors was similar across the treatment groups with patients most commonly suffering from hypertension (46%), followed by hypercholesterolemia (29%) and diabetes mellitus (12%). Similar effects in reduction of moderate and severe exacerbations were observed in this subgroup as compared with the overall population. In patients with a cardiovascular history/risk factors, fluticasone furoate/vilanterol 92/22 micrograms resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with vilanterol (adjusted mean annual rates of 0.83 and 1.18 respectively, 30% reduction (95% CI 16, 42%, p<0.001)). Improvements were also seen in this subgroup at Week 52 when comparing the fluticasone furoate/vilanterol 92/22 micrograms vs. vilanterol 22 micrograms in adjusted mean trough FEV_1 (44 mL 95% CI: 15, 73 mL, (p=0.003)).

Studies > 1 year duration

SUMMIT was a multi-centre, randomised, double-blind study evaluating the effect on survival of fluticasone furoate/vilanterol 92/22 micrograms compared with placebo in 16,485 subjects. The primary endpoint was all-cause mortality and a secondary endpoint was a composite of cardiovascular events (on-treatment cardiovascular death, myocardial infarction, stroke, unstable angina, or transient ischemic attack).

Prior to randomization, subjects were required to discontinue previous COPD medications used at baseline, which included long-acting bronchodilators plus inhaled corticosteroids (28%), long-acting bronchodilators alone (11%) and inhaled corticosteroids alone (4%). Subjects were then randomized to receive either fluticasone furoate/vilanterol 92/22 micrograms, fluticasone furoate 92 micrograms, vilanterol 22 micrograms, or placebo, and treated for a mean of 1.7 years (SD = 0.9 years).

Subjects had moderate COPD (mean percent post-bronchodilator screening FEV_1 of 60% [SD = 6%]), and a history of, or an increased risk of cardiovascular disease. In the 12 months prior to the study, 61% of subjects reported no COPD exacerbations and 39% of subjects reported ≥1 moderate/severe COPD exacerbation.

All-cause mortality was: fluticasone furoate/vilanterol, 6.0%; placebo, 6.7%; fluticasone furoate, 6.1%; vilanterol, 6.4%. Exposure-adjusted all-cause mortality per 100 patients/year (%/yr) was: fluticasone furoate/vilanterol, 3.1 %/yr; placebo, 3.5 %/yr; fluticasone furoate, 3.2 %/yr; and vilanterol, 3.4 %/yr. Mortality risk with fluticasone furoate/vilanterol was not significantly different compared with placebo (HR 0.88; 95% CI: 0.74 to 1.04; p=0.137), fluticasone furoate (HR 0.96; 95% CI: 0.81 to 1.15; p=0.681) or vilanterol (HR 0.91; 95% CI: 0.77 to 1.09; p=0.299).

The risk of the cardiovascular composite event with fluticasone furoate/vilanterol was not significantly different compared with placebo (HR 0.93; 95% CI: 0.75 to 1.14), fluticasone furoate (HR 1.03; 95% CI: 0.83 to 1.28) or vilanterol (HR 0.94; 95% CI: 0.76 to 1.16).

Studies versus salmeterol/fluticasone propionate combinations

In a 12 week study (HZC113107) in COPD patients both fluticasone furoate/vilanterol 92/22 micrograms given once daily in the morning and salmeterol/FP 50/500 micrograms given twice daily, demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV_1 of 130 mL (fluticasone furoate/vilanterol) and 108 mL (salmeterol/FP) demonstrated an overall improvement in lung function over 24 hours for both treatments. The adjusted mean treatment difference of 22 mL (95% CI: -18, 63 mL) between the groups was not statistically significant (p=0.282). The adjusted mean change from baseline in trough FEV_1 on Day 85 was 111 mL in the fluticasone furoate/vilanterol group and 88 mL in the salmeterol/FP group; the 23 mL (95% CI: -20, 66) difference between the treatment groups was not clinically meaningful or statistically significant (p=0.294).
No comparative studies versus salmeterol/FP or versus other established bronchodilators have been conducted to appropriately compare the effects on COPD exacerbations.

Paediatric population

Asthma

The efficacy and safety of fluticasone furoate (FF)/vilanterol (VI) administered once daily compared to FF administered once daily in the treatment of asthma in paediatric patients aged 5-11 years was evaluated in a randomised, double-blind, multicentre clinical trial of 24 weeks duration and 1 week follow-up period (HZA107116) involving 673 patients with uncontrolled asthma, on inhaled corticosteroids.
All subjects had stable asthma therapy [short-acting beta agonist or short-acting muscarinic antagonist inhaler plus inhaled corticosteroid (ICS)] for at least 4 weeks prior to Visit 1. Patients were symptomatic (i.e., remained uncontrolled) on their existing asthma treatment.
Subjects were treated with fluticasone furoate/vilanterol 46/22 micrograms (337 patients) or fluticasone furoate 46 micrograms (336 patients). Two patients, one in each arm, were not assessable for efficacy.
The primary endpoint was change from baseline, averaged over weeks 1 to 12 of the treatment period, in pre-dose (i.e., trough) morning peak expiratory flow (PEF), captured daily via electronic patient diary (difference between FF/VI combination and FF). Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1 to 12 of the treatment period was a powered secondary endpoint for the 5-11 years population. There were no differences in efficacy between FF/VI 46/22 micrograms and FF 46 micrograms (Table 3). No new safety concerns were identified during this study.

Table 3: Results of primary and powered secondary endpoints in HZA107116

Weeks 1 to 12	Fluticasone furoate/Vilanterol* n=336	Fluticasone furoate* n=335
Primary endpoint		
Change from Baseline in AM PEF (L/min)		
LS Mean Change (SE)	12.0 (1.86)	8.8 (1.86)
Treatment difference (FF/VI vs FF) (95% CI), p-value	3.2 (-2.0, 8.4), p=0.228	
Powered secondary endpoint		
Change from Baseline in Percentage of Rescue-free 24-hour Periods		
LS Mean Change (SE)	27.1 (1.75)	25.8 (1.75)
Treatment difference (FF/VI vs FF) (95% CI), p-value	1.3 (-3.6, 6.2), p=0.614	

*Patients were receiving FF/VI 46/22 micrograms OD vs FF 46 micrograms OD
OD = Once Daily, LS = least squares, SE = standard error, CI = confidence interval, n = number of participants in analysis (All ITT: 337 for FF/VI and 336 for FF)

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability for fluticasone furoate and vilanterol when administered by inhalation as fluticasone furoate/vilanterol was on average 15.2% and 27.3%, respectively. The oral bioavailability of both fluticasone furoate and vilanterol was low, on average 1.26% and <2%, respectively. Given this low oral bioavailability, systemic exposure for fluticasone furoate and vilanterol following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Distribution

Following intravenous dosing, both fluticasone furoate and vilanterol are extensively distributed with average volumes of distribution at steady state of 661 L and 165 L, respectively.
Both fluticasone furoate and vilanterol have a low association with red blood cells. In vitro plasma protein binding in human plasma of fluticasone furoate and vilanterol was high, on average >99.6% and 93.9%, respectively. There was no decrease in the extent of in vitro plasma protein binding in subjects with renal or hepatic impairment.
Fluticasone furoate and vilanterol are substrates for P-glycoprotein (P-gp), however, concomitant administration of fluticasone furoate/vilanterol with P-gp inhibitors is considered unlikely to alter fluticasone furoate or vilanterol systemic exposure since they are both well absorbed molecules.

Biotransformation

Based on *in vitro* data, the major routes of metabolism of both fluticasone furoate and vilanterol in human 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. Vilanterol is primarily metabolised by O-dealkylation to a range of metabolites with significantly reduced β_1- and β_2-agonist activity.

Elimination

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.

Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively in a human radiolabel study conducted by the oral route. The apparent plasma elimination half-life of vilanterol following single inhaled administration of fluticasone furoate/vilanterol was, on average, 2.5 hours. The effective half-life for accumulation of vilanterol, as determined from inhalation administration of repeat doses of vilanterol 25 micrograms, is 16.0 hours in subjects with asthma and 21.3 hours in subjects with COPD.

Paediatric population

In adolescents (12 years or older), there are no recommended dose modifications.

The pharmacokinetics, safety and efficacy of fluticasone furoate/vilanterol have been studied in children from 5 to 11 years old, but no recommendation on a posology can be made (see section 4.2). The pharmacokinetics, safety and efficacy of fluticasone furoate/vilanterol in children under the age of 5 years have not been established.

Special populations

Elderly

The effects of age on the pharmacokinetics of fluticasone furoate and vilanterol were determined in phase III studies in COPD and asthma. There was no evidence for age (12 to 84 years) to affect the pharmacokinetics of fluticasone furoate and vilanterol in subjects with asthma.

There was no evidence for age to affect the pharmacokinetics 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} was unchanged. These differences are unlikely to be of clinical relevance.
In elderly subjects with asthma and elderly subjects with COPD there are no recommended dose modifications.

Renal impairment

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.

No dose adjustment is required for patients with renal impairment.

The effects of haemodialysis have not been studied.

Hepatic impairment

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0–24)}$) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (Child-Pugh B; fluticasone furoate/vilanterol 184/22 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. Dose-normalised fluticasone furoate systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B or C).

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, 22 micrograms) or with severe hepatic impairment (vilanterol, 12.5 micrograms) compared with healthy subjects.

Other special populations

In subjects with asthma, estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects (12-13% of subjects) were on average 33% to 53% higher compared with other racial groups. 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. On average, vilanterol C_{max} is predicted to be 220 to 287% higher and $AUC_{(0-24)}$ comparable for those subjects from an Asian heritage compared with subjects from other racial groups. However, there was no evidence that this higher vilanterol C_{max} resulted in clinically significant effects on heart rate.
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 pharmacokinetic parameter estimates of vilanterol in subjects with COPD.

Gender, weight and BMI

There was no evidence for gender, weight or BMI (body mass index) to influence the pharmacokinetics of fluticasone furoate based on a population pharmacokinetic analysis of phase III data in 1213 subjects with asthma (712 females) and 1225 subjects with COPD (392 females).

There was no evidence for gender, weight or BMI to influence the pharmacokinetics of vilanterol based on a population pharmacokinetic analysis in 856 subjects with asthma (500 females) and 1091 subjects with COPD (340 females).

No dosage adjustment is necessary based on gender, weight or BMI.

5.3 Preclinical safety data

Pharmacological and toxicological effects seen with fluticasone furoate or vilanterol in non-clinical studies were those typically associated with either glucocorticoids or $beta_2$-agonists. Administration of fluticasone furoate combined with vilanterol did not result in any significant new toxicity.

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 similar to those at the maximum recommended human dose, based on AUC.

Vilanterol trifenatate

In genetic toxicity studies, 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 1.2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Toxicity to reproduction and development

Fluticasone furoate

Effects seen following inhalation administration of fluticasone furoate in combination with vilanterol in rats were similar to those seen with fluticasone furoate alone.
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 approximately 3-times greater than those at the maximum recommended human dose, based on AUC.

Vilanterol trifenatate

Vilanterol trifenatate was not teratogenic in rats. In inhalation studies in rabbits, vilanterol trifenatate caused effects similar to those seen with other beta$_2$ agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 84-times greater than those at the maximum recommended human dose, based on AUC.
Neither fluticasone furoate nor vilanterol trifenatate had any adverse effects on fertility or pre- and 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 of the product is indicated on the packaging materials.

In-use shelf-life after opening the tray: 6 weeks, but not later than the expiry date.

6.4 Special precautions for storage

Do not store above 25°C. If stored in a refrigerator allow the inhaler to return to room temperature for at least an hour before use.

Store in the original package in order to protect from moisture.

Write the date 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, a pale blue 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).

Pack sizes of 14 or 30 dose Inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MANUFACTURER

Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations), Ware, UK.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

Relvar Ellipta 92/22 mcg: 151-45-33982
Relvar Ellipta 184/22 mcg: 151-46-33981

Revised in January 2024.

Relv DR v14