

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 200/25 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients 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 with a pale blue mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Relvar Ellipta 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 beta₂-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta₂-agonists.

4.2 Posology and method of administration

Posology

Asthma

Adults and adolescents aged 12 years and over

One inhalation of Relvar Ellipta 200/25 micrograms once daily.

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 beta₂-agonist should be taken for immediate relief.

A starting dose of Relvar Ellipta 100/25 micrograms 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

beta₂-agonist. If patients are inadequately controlled on Relvar Ellipta 100/25 micrograms, the dose can be increased to 200/25 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 200/25 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 beta₂-agonist.

The maximum recommended dose is Relvar Ellipta 200/25 micrograms once daily.

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.

Children aged under 12 years

The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the indication for asthma.
No data are available.

Special populations

Elderly patients (>65 years)

No dose adjustment is required in this population (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 100/25 micrograms (see section 4.4).

Method of administration

Relvar Ellipta is for inhalation use 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.

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.

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

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. Once opened the desiccant sachet should be discarded.

The patient should be advised to not open the tray until they are ready to inhale a dose.

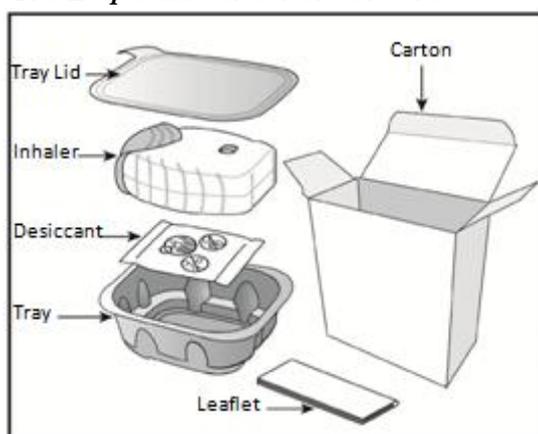
When the inhaler is taken out of its tray, it will be in the 'closed' position. The "Discard by" date should be written on the inhaler label in the space provided. The "Discard by" date is 1 month from the date of opening the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

Instructions for use

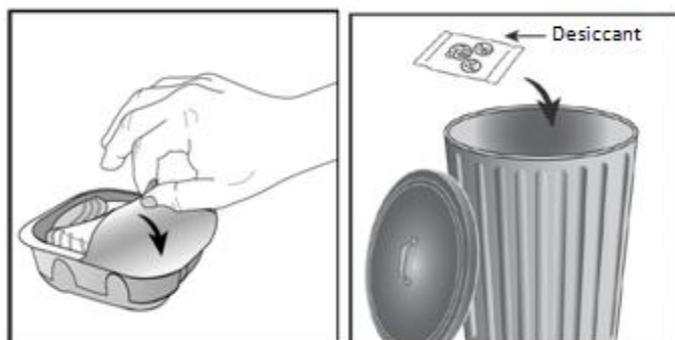
The ELLIPTA inhaler contains pre-dispensed doses and is ready to use.

When the patient first uses the Ellipta inhaler the patient does not need to check that it is working properly, and the patient does not need to prepare it for use in any special way. The patient just has to follow the instructions below.

The Ellipta inhaler carton contains



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



The inhaler will be in the 'closed' position when it is first taken out of its sealed tray. The patient should be advised not to open the inhaler until ready to inhale a dose of medicine. The "Discard by" date should be written on the inhaler label in the space provided. The "Discard by" date is 1 month 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.

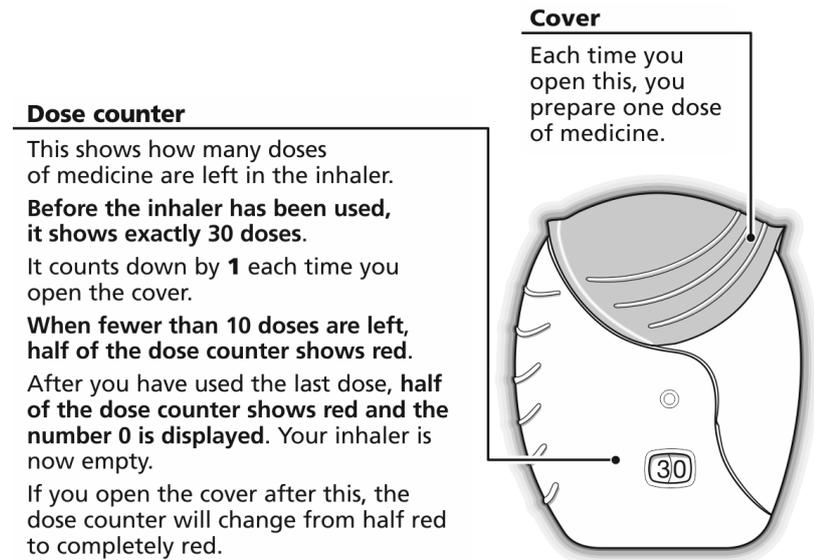
If the inhaler cover is opened and closed without inhaling the medicinal product, the dose will be lost. The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled.

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

a) Read this before you start

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

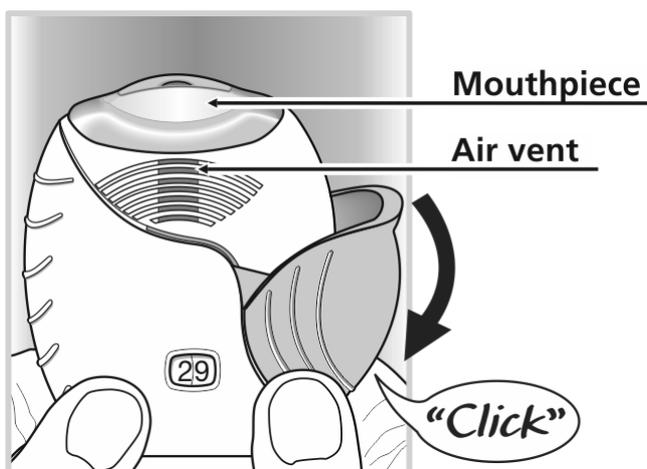
It is not possible to accidentally take extra medicine or a double dose in one inhalation.



b) How to prepare a dose

Open the cover when ready to take a dose. **Do not shake the inhaler.**

Slide the cover down until you hear a 'click'.



The medicine is now ready to be inhaled.

The dose counter counts down by 1 to confirm.

If the dose counter does not count down as you hear the ‘**click**’, the inhaler will not deliver medicine. Take it back to a pharmacist for advice.

Do not shake the inhaler at any time.

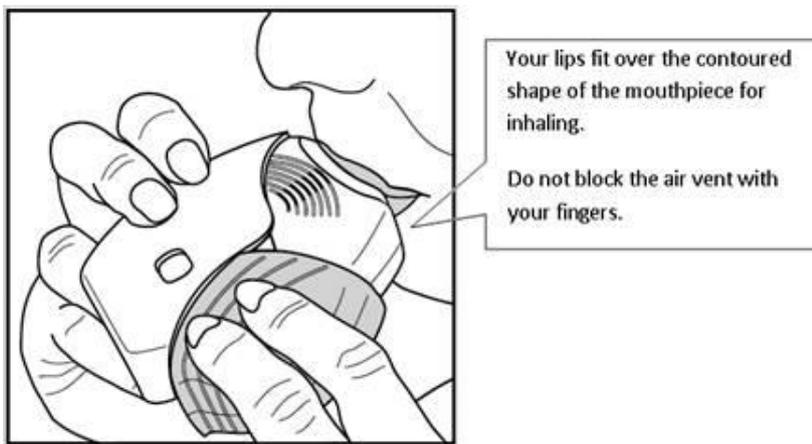
c) How to inhale the medicine

Hold the inhaler away from your mouth and breathe out as far as is comfortable.

Do not breathe out into the inhaler.

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

Do not block the air-vents with your fingers.



Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).

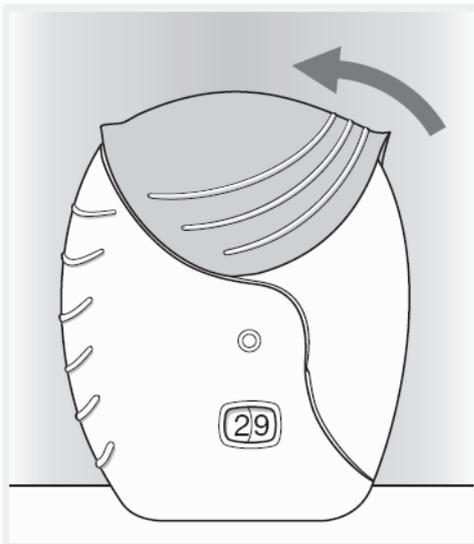
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

It may not be possible to taste or feel the medicine, even when using the inhaler correctly.

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

d) Close the inhaler and rinse your mouth

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



Rinse your mouth with water after you have used the inhaler.

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, 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, 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 a history of, or an increased risk of, cardiovascular disease, there was no increase in the risk of, cardiovascular events, serious cardiovascular events, or adjudicated cardiovascular deaths in patients receiving fluticasone furoate/vilanterol compared with placebo (see Adverse Reactions). 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 100/25 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.

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.

Relvar Ellipta 200/25 micrograms is not indicated for patients with COPD. There is no additional benefit of the 200/25 micrograms dose compared to the 100/25 micrograms dose and there is a potential increased risk of systemic corticosteroid-related adverse reactions (see section 4.8).

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 200/25 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 100/25 micrograms or placebo (see section 4.8). No risk factors were identified.

Excipients

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take 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

Beta₂-adrenergic blockers may weaken or antagonise the effect of beta₂-adrenergic agonists. Concurrent use of both non-selective and selective beta₂-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) as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, and concomitant use should be avoided. A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25 micrograms) and the strong CYP3A4 inhibitor ketoconazole (400mg). 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 beta₂-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 beta₂-adrenergic agonists or medicinal products containing long-acting beta₂-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 trifenate 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 trifenate and/or metabolites in human milk. However, other corticosteroids and beta₂ 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 trifenate 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 program 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 commonly 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
Nervous system disorders	Headache Tremor	Very common Rare
Psychiatric disorders	Anxiety	Rare
Cardiac disorders	Extrasystoles** Palpitations Tachycardia	Uncommon Rare Rare
Respiratory, thoracic and mediastinal disorders	Nasopharyngitis Paradoxical bronchospasm Oropharyngeal pain Sinusitis Pharyngitis Rhinitis Cough Dysphonia	Very common Rare Common
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

*, ** and *** See below ‘Description of selected adverse reactions’

Description of selected adverse reactions

*Pneumonia (see Warnings and Precautions)

In an integrated analysis of the two replicate one year studies in COPD (mean post-bronchodilator screening FEV₁ 45% of predicted, 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 200/25, 85.7 in the FF/VI 100/25 and 42.3 in the VI 25 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 200/25, 42.9 with FF/VI 100/25, 12.1 with VI 25. Finally, the

exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 200/25 versus 1.5 for FF/VI 100/25 and 0 for VI 25.

In SUMMIT, a multi-centre, randomised study (HZC113782), 16,568 subjects received fluticasone furoate/vilanterol 92/22 micrograms, fluticasone furoate 92 micrograms, vilanterol 22 micrograms, or placebo for a mean of 1.7 years. Subjects had moderate COPD (mean post-bronchodilator screening FEV₁ 60% of predicted, SD 6%) and a history of, or an increased risk of, cardiovascular disease. The adverse events of pneumonia are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 92/22 N=4,140	FF 92 N=4,157	VI 22 N=4,140	Placebo N=4,131
Pneumonia	237 (6) [39.5]	228 (5) [42.4]	163 (4) [27.7]	214 (5) [38.4]
Serious pneumonia	140 (3) [22.4]	146 (4) [25.1]	104 (3) [16.4]	127 (3) [22.2]
Adjudicated pneumonia deaths	13 (<1) [1.8]	10 (<1) [1.5]	6 (<1) [0.9]	9 (<1) [1.4]

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 200/25 versus 9.6 for FF/VI 100/25 and 8.0 in the placebo group.

**Cardiovascular events (see section 4.4)

For the SUMMIT study, cardiovascular adverse events are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 92/22 N=4,140	FF 92 N=4,157	VI 22 N=4,140	Placebo N=4,131
Cardiovascular	735 (18) [163]	699 (17) [157]	707 (17) [157]	695 (17) [164]
Serious cardiovascular	350 (8) [64.5]	320 (8) [58.1]	337 (8) [59.2]	318 (8) [63.2]
Adjudicated cardiovascular deaths	82 (2) [11.7]	80 (2) [11.6]	90 (2) [12.9]	86 (2) [13.0]

***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 25 micrograms group (<1%). Although there were more fractures in the Relvar Ellipta groups compared with the vilanterol 25 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, fractures are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 92/22 N=4,140	FF 92 N=4,157	VI 22 N=4,140	Placebo N=4,131
All fractures	82 (2) [13.6]	66 (2) [12.8]	74 (2) [13.2]	69 (2) [11.5]
Fractures commonly associated with ICS use	23 (<1) [3.4]	24 (<1) [3.9]	17 (<1) [2.4]	13 (<1) [2.1]

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. Healthcare professionals are asked to report any suspected adverse reactions to the National Centre for Adverse Drug Reaction Monitoring, National Pharmaceutical Regulatory Agency (NPRA).

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 beta₂-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 and other drugs for obstructive airway diseases, ATC code: R03AK10.

Mechanism of action

Fluticasone furoate and vilanterol represent two classes of medications (a synthetic corticosteroid and a selective, long-acting beta₂-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 trifenate

Vilanterol trifenate is a selective long-acting, beta₂-adrenergic agonist (LABA).

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including vilanterol trifenate, 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 beta₂-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.

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 100/25 micrograms [n=201] and FF 100 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 200/25 micrograms [n=197] and FF 200 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) FEV₁ at the end of the treatment period in all subjects and weighted mean serial FEV₁ 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 200/25 Once Daily vs FF 200 Once Daily	FF/VI 200/25 Once Daily vs FP 500 Twice Daily	FF/VI 100/25 Once Daily vs FF 100 Once Daily
Change from Baseline in Trough FEV₁ Last Observation Carried Forward (LOCF)				
Treatment difference	193mL	210mL	36mL	172mL

Study No.	HZA106829		HZA106827	
P value (95% CI)	p<0.001 (108, 277)	p<0.001 (127, 294)	p=0.405 (-48, 120)	p<0.001 (87, 258)
Weighted Mean Serial FEV₁ over 0-24 hours post-dose				
Treatment difference	136mL	206mL	116mL	302mL
P value (95% CI)	p=0.048 (1, 270)	p=0.003 (73, 339)	p=0.06 (-5, 236)	p<0.001 (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 (95% CI)	p<0.001 (4.9, 18.4)	p=0.067 (-0.4, 13.1)	p<0.001 (4.3, 16.8)	p<0.001 (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 (95% CI)	p=0.010 (2.0, 14.8)	p=0.137 (-1.6, 11.3)	p<0.001 (6.2, 18.1)	p<0.001 (12.0, 23.9)
Change from Baseline in AM Peak Expiratory Flow				
Treatment difference	33.5L/min	32.9L/min	14.6L/min	33.3L/min
P value (95% CI)	p<0.001 (22.3, 41.7)	p<0.001 (24.8, 41.1)	p<0.001 (7.9, 21.3)	p<0.001 (26.5, 40.0)
Change from Baseline in PM Peak Expiratory Flow				
Treatment difference	30.7L/min	26.2L/min	12.3L/min	28.2L/min
P value (95% CI)	p<0.001 (22.5, 38.9)	p<0.001 (18.0, 34.3)	p<0.001 (5.8, 18.8)	p<0.001 (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 100/25 micrograms [n=1009] or FF 100 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 FEV₁ was also evaluated as a secondary endpoint.

In HZA106837 the risk of experiencing a severe asthma exacerbation in patients receiving fluticasone furoate/vilanterol 100/25 micrograms was reduced by 20% compared with FF 100 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 100 micrograms group (approximately 1 in every 5 years) and 0.14 in the fluticasone furoate/vilanterol 100/25 micrograms group (approximately 1 in every 7 years). The ratio of the exacerbation rate for fluticasone furoate/vilanterol 100/25 micrograms versus FF 100 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 100/25 micrograms compared with FF 100 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 100/25 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV₁ at weeks 12, 36 and 52 and Endpoint compared with FF 100 micrograms (p<0.001 95% CI 52, 126 mL at Endpoint). Forty four percent of patients in the fluticasone furoate/vilanterol 100/25 group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 100 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 persistent asthma both fluticasone furoate/vilanterol 100/25 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 FEV₁ 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 FEV₁ subjects in the fluticasone furoate/vilanterol group achieved a LS mean change from baseline of 281 mL and subjects in 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).

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

Fluticasone furoate monotherapy

A 24 week randomised, double-blind placebo controlled study (FFA112059) evaluated the safety and efficacy of FF 100 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) FEV₁ 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 FEV₁ 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 100/25 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 100/25 micrograms, FF 100 micrograms, vilanterol 25 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 FEV₁ 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 100/25 micrograms compared with FF 100 micrograms or vilanterol 25 micrograms alone. Both fluticasone furoate/vilanterol 100/25 micrograms and FF 100 micrograms virtually abolished the late asthmatic response compared with vilanterol alone. Fluticasone furoate/vilanterol 100/25 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.

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 of fluticasone furoate/vilanterol in patients less than 12 years of age has not been studied. The safety and efficacy of fluticasone furoate/vilanterol in children under the age of 12 years has not yet been established.

Special populations

Elderly patients (> 65 years old)

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 (12-84) to affect the pharmacokinetics of fluticasone furoate and vilanterol in subjects with asthma.

In subjects with asthma and 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 <30mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or beta₂-agonist systemic effects compared with healthy subjects.

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 200/25 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child Pugh C) that received a lower dose of 100/2.5 micrograms there was no reduction in serum cortisol. For patients with moderate or severe hepatic impairment the maximum dose of 100/25 micrograms (see Dosage and Administration).

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

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

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.

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).

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).

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 nonclinical studies were those typically associated with either glucocorticoids or beta₂-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 trifenate

In genetic toxicity studies, vilanterol (as alpha-phenylcinnamate) and triphenylacetic acid were not genotoxic indicating that vilanterol (as trifenate) does not represent a genotoxic hazard to humans.

Consistent with findings for other beta₂ agonists, in lifetime inhalation studies vilanterol trifenate 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 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Reproductive toxicity

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 trifenate

Vilanterol trifenate was not teratogenic in rats. In inhalation studies in rabbits, vilanterol trifenate caused effects similar to those seen with other beta₂ 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 trifenate 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

2 years

In-use shelf-life: 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.

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

To be used within 1 month of first opening of the tray.

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

6.5 Nature and contents of container

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

The inhaler contains two aluminium foil laminate strips of 14 or 30 doses.

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

Pack sizes of 14 or 30 dose Inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

For instructions for use, see section 4.2.

7. PRODUCT REGISTRATION HOLDER

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8. MANUFACTURER

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