RELVAR™ ELLIPTA™
Fluticasone furoate/vilanterol

QUALITATIVE AND QUANTITATIVE COMPOSITION
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) or 184 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) or 200 micrograms of fluticasone furoate and 25 micrograms vilanterol (as trifenatate), respectively.
Excipients with known effect:
Each delivered dose contains approximately 25 mg of lactose (as monohydrate).
PHARMACEUTICAL FORM
Inhalation powder, pre-dispensed.
White powder in a light grey inhaler with a pale blue mouthpiece cover and a dose counter.
CLINICAL PARTICULARS
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 beta$_2$-agonist and inhaled corticosteroid) is appropriate:
- patients not adequately controlled with inhaled corticosteroids and 'as needed' inhaled short acting beta$_2$-agonists.

COPD (Chronic Obstructive Pulmonary Disease)
RELVAR ELLIPTA 100 micrograms/25 micrograms inhalation powder 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.
Dosage and Administration
Posology
Asthma
Adults and adolescents aged 12 years and over
One inhalation of *RELVAR ELLIPTA* 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 beta$_2$-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 beta$_2$-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 beta$_2$-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.
COPD
Adults aged 18 years and over
One inhalation of *RELVAR ELLIPTA* 100/25 micrograms once daily.
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 pneumonia and systemic corticosteroid-related adverse reactions.
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 in the indication for COPD.
Special populations
Elderly patients (>65 years)
No dose adjustment is required in this population.
Renal impairment
No dose adjustment is required in this population.
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).
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.
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 atleast an hour before use.
After inhalation, patients should rinse their mouth with water without swallowing.
See *Nature and Contents of Container* and *Instructions for Use/Handling*
Contraindications
RELVAR ELLIPTA is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol or any of the excipients.
Warnings and Precautions
Exacerbations:
RELVAR ELLIPTA 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 *RELVAR ELLIPTA*, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.
Asthma-related adverse events and exacerbations may occur during treatment with RELVAR ELLIPTA. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of RELVAR ELLIPTA.
Paradoxical bronchospasm
As with other inhalation therapy, 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 drugs, including *RELVAR ELLIPTA*. Therefore *RELVAR ELLIPTA* should be used with caution in patients with severe cardiovascular disease.
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 Dosage and Administration, Pharmacokinetics).
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, HPA axis suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma.
As with all medication containing corticosteroids, *RELVAR ELLIPTA* should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.
Pneumonia
An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation.
In some incidences these pneumonia events were fatal (see *Clinical studies and Adverse Reactions*). 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 receiving *RELVAR ELLIPTA* include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m² and patients with a (forced expiratory volume) FEV_1<50% predicted. These factors should be considered when fluticasone furoate/vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs.
The incidence of pneumonia in patients with asthma was uncommon. Patients with asthma taking fluticasone furoate/vilanterol 200/25 micrograms may be at an increased risk of pneumonia compared with those receiving fluticasone furoate/vilanterol 100/25 or placebo.
No risk factors were identified.
Interactions
Clinically significant drug interactions mediated by fluticasone furoate or vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.
Interaction with beta-blockers
Beta-adrenergic blockers may weaken or antagonise the effect of beta$_2$-adrenergic agonists. Concurrent use of both non-selective and selective beta-blockers should be avoided unless there are compelling reasons for their use.
Interaction with CYP3A4 inhibitors
Fluticasone furoate and vilanterol are both rapidly cleared by extensive first-pass metabolism mediated by the liver enzyme CYP3A4.
Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see *Pharmacokinetics*).
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.
Pregnancy and Lactation
Fertility
There are no fertility data in humans. Animal studies showed no effect of vilanterol or fluticasone furoate on fertility (see *Non-clinical Information* section).
Pregnancy
There has been limited pregnancy exposure in humans.
Animal studies have shown reproductive toxicity after administration of beta$_2$-agonists and corticosteroids (see *Non-clinical Information* section).
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.
Lactation
There is limited information on the excretion of fluticasone furoate or vilanterol or their metabolites in human milk. However, other corticosteroids and beta$_2$-agonists are detected in human milk (see *Non-clinical Information* section). A risk to breastfed newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue *RELVAR ELLIPTA* therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Ability to perform tasks that require Judgement, Motor or Cognitive Skills
There have been no studies to investigate the effect of fluticasone furoate/vilanterol on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of fluticasone furoate or vilanterol.
Adverse Reactions
Clinical trial data
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 program a total of 6,237 subjects were included in an integrated assessment of adverse reactions.
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.
These adverse events are listed by system organ class and frequency. The following convention has been used for the classification of adverse reactions:
Very common: ≥1/10
Common: ≥1/100 to <1/10
Uncommon: ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Pneumonia*, Upper Respiratory Tract Infection, Bronchitis, Influenza, Candidiasis of mouth and throat	Common
Nervous system disorders	Headache	Very Common
Cardiac disorders	Extrasystoles	Uncommon
Respiratory, thoracic & mediastinal disorders	Nasopharyngitis Oropharyngeal pain, Sinusitis, Pharyngitis. Rhinitis, Cough, Dysphonia	Very Common Common
Gastrointestinal disorders	Abdominal pain	Common
Musculoskeletal and connective tissue disorders	Arthralgia, Back pain, Fractures**	Common
General disorders and administration site conditions	Pyrexia	Common

Description of selected adverse reactions
*Pneumonia
In two replicate 12 month studies in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the fluticasone furoate (at strengths of 50, 100 and 200 micrograms)/vilanterol 25 micrograms combination than in those receiving vilanterol 25 micrograms alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving fluticasone furoate/vilanterol (all strengths) and in <1% of patients receiving vilanterol. In these studies, nine fatal cases of pneumonia were reported. Of these, seven were reported during treatment with fluticasone furoate/vilanterol 200/25 micrograms, one during treatment with fluticasone furoate/vilanterol 100/25 micrograms and one post-treatment with vilanterol monotherapy. Risk factors for pneumonia observed in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m² and patients with an FEV_1 <50% predicted (see *Warnings and Precautions*).
In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with fluticasone furoate/vilanterol 100/25 microgram strength (9.6/1000 patient years) was similar to placebo (8.0/1000 patient years). There was a higher incidence of pneumonia in the 200/25 microgram strength (18.4/1000 patient years) compared to the 100/25 microgram strength. Few of the pneumonia events led to hospitalisation with either strength, and there were no observed differences in the incidence of serious events between the two treatment strengths.
**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 fluticasone furoate/vilanterol groups (2%) compared with the vilanterol 25 micrograms group (<1%). Although there were more fractures in the fluticasone furoate/vilanterol 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 fluticasone furoate/vilanterol and vilanterol treatment arms.
In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures was <1%, and usually associated with trauma.
Post-marketing data

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

Overdose
Symptoms and signs
There are no data available from clinical trials on overdose with fluticasone furoate/vilanterol. An overdose of *RELVAR ELLIPTA* may produce signs and symptoms due to the individual components' actions, including those seen with overdose of other beta$_2$-agonists and consistent with the known inhaled corticosteroid class effects (see *Warnings and Precautions*).
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 drugs 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.
CLINICAL PHARMACOLOGY
Pharmacodynamics
ATC Code
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 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 drugs, 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 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. Airway biopsy studies have also shown the synergy between corticosteroids and LABAs to occur at clinical doses of the drugs in patients with COPD.
Pharmacokinetics
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-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.
Metabolism
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.
A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25) 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 h 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-agonist related systemic effects on heart rate, blood potassium or QTcF interval.
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. The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of fluticasone furoate/vilanterol was, on average, 24 hours.
Following oral administration, vilanterol was eliminated in humans mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively. The apparent plasma elimination half-life of vilanterol following inhaled administration of fluticasone furoate/vilanterol was, on average, 2.5 hours.
Special Patient Populations
Population PK meta-analyses for fluticasone furoate and vilanterol were conducted in phase III studies in subjects with asthma or COPD. The impact of demographic covariates (age, gender, weight, BMI, racial group, ethnicity) on the pharmacokinetics of fluticasone furoate and vilanterol were evaluated as part of the population pharmacokinetic analysis.
Race
In subjects with asthma or COPD estimates of fluticasone furoate AUC(0-24) for East Asian, Japanese and South East Asian subjects (12-14% subjects) were up to 53% higher on average compared with Caucasian subjects. However, there was no evidence for the higher systemic exposure in these populations 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.
On average, vilanterol C_{max} is estimated 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.
Children
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.
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 (12-84) to affect the PK of fluticasone furoate and vilanterol in subjects with asthma.
There was no evidence for age to affect the PK of fluticasone furoate in subjects with COPD while there was an increase (37%) in AUC (0-24) of vilanterol over the observed age range of 41 to 84 years. For an elderly subject (aged 84 years) with low bodyweight (35 kg) vilanterol AUC (0-24) is predicted to be 35% higher than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg), whilst C_{max} was unchanged. These differences are unlikely to be of clinical relevance.
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 cardiovascular 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 (fluticasone furoate/vilanterol 200/25 micrograms) in subjects with moderate hepatic impairment (Child-Pugh B) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child-Pugh C) that received a lower dose of 100/12.5 micrograms there was no reduction in serum cortisol For patients with moderate or severe hepatic impairment the maximum dose is 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.
Gender, Weight and BMI
There was no evidence for gender, weight or BMI 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 body mass index (BMI).
Clinical Studies
Fluticasone furoate/vilanterol clinical studies
Asthma
The safety and efficacy of fluticasone furoate (FF) and vilanterol (VI) in the treatment of asthma has been evaluated in 3 randomised, double-blind clinical trials of between 12 to 76 weeks in duration (HZA106827, HZA106829 and HZA106837) involving 3,210 patients 12 years of age and older 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. Results for HZA106827 and HZA106829 are shown in the table below:
Summary of Data from Studies HZA106829 and HZA106827

Study No.	HZA106829	HZA106827		
	FF/VI 200/25 OD* vs FF 200 OD	FF/VI 100/25 OD vs FF 100 OD	FF/VI 100/25 OD vs placebo OD	FF 100 OD vs placebo OD
Change from Baseline in Trough FEV1 (mL)				
Treatment difference (95% CI)	193 (108, 277)	36 (-48, 120)	172 (87, 258)	136 mL(51, 222)
p-value	p<0.001	p=0.405	p<0.001	p=0.002
Weighted Mean Serial FEV1 over 0-24 hours post-dose (mL)				
Treatment difference (95% CI)	136 (1, 270)	116 (-5, 236)	302 (178, 426)	186 mL(62, 310)
p-value	p=0.048	p=0.06	p<0.001	p=0.003
Change from Baseline in Rescue–free 24 hour periods				
Treatment difference (95% CI)	11.7% (4.9, 18.4)	10.6% (4.3, 16.8)	19.3% (13.0, 25.6)	8.7% (2.4, 15.0)
p-value	p<0.001	p<0.001	p<0.001	p=0.007

*OD = Once Daily
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) and compared FF/VI 100/25 micrograms [N=1009] and FF 100 micrograms [N=1010]. 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 or an inpatient hospitalization or emergency department visit.
The risk of experiencing a severe asthma exacerbation in patients receiving FF/VI 100/25 was reduced by 20% compared with FF 100 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 group and 0.14 in the FF/VI 100/25 group. The ratio of the exacerbation rate for FF/VI 100/25 versus FF 100 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 FF/VI 100/25 compared with FF 100 (p=0.014). The 24-hour bronchodilator effect of FF/VI was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). FF/VI 100/25 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV_1 at Weeks 12, 36 and 52 and Endpoint compared with FF 100 (p<0.001 95% CI 52, 126mL at Endpoint). Forty four percent of patients in the FF/VI 100/25 group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 100 group (p<0.001 95% CI 1.23, 1.82).
Chronic Obstructive Pulmonary Disease
The efficacy of fluticasone furoate and vilanterol in the treatment of patients with COPD has been evaluated in two 6-month (HZC112206, HZC112207) and two one-year randomised controlled studies (HZC102970, HZC102871) in patients with a clinical diagnosis of COPD.
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 FF/VI 50/25 micrograms [n=206] and FF/VI 100/25 micrograms [n=206]) compared with FF (100 micrograms [n=206]) and vilanterol (25 micrograms [n=205]) and placebo (n = 207), all administered once daily. HZC112207 evaluated the efficacy of FF/VI 100/25 micrograms [n=204] and FF/VI 200/25 [n=205]) compared with FF (100 micrograms [n=204] and 200 micrograms [n=203]) and vilanterol (25 micrograms [n=203]) and placebo (n = 205), all administered once daily.
The co-primary endpoints in both studies were the weighted mean FEV_1 from zero to 4 hours post-dose and change from baseline in pre-dose trough FEV_1 at the end of the study. In an integrated analysis of both studies, FF/VI 100/25 micrograms showed clinically meaningful improvements in lung function. At the 24-week time point FF/VI 100/25 micrograms and vilanterol increased trough FEV_1 by 129 mL (95% CI 91, 167 mL, p<0.001) and 83mL (95% CI 46, 121mL, p<0.001) respectively compared with placebo. FF/VI 100/25 micrograms increased trough FEV_1 by 46 ml compared with vilanterol (95% CI 8, 83mL, p= 0.017).
At the 24-week time point FF/VI 100/25 micrograms and vilanterol had a higher weighted mean FEV_1 over 0-4 hours of 193 mL (95% CI 156, 230mL, p<0.001) and 145 mL (95% CI 108, 181mL, p<0.001) respectively compared with placebo. The difference in weighted mean FEV_1 over 0-4 hours between the FF/VI 100/25 and vilanterol groups was 48 (95 CI 12, 84 mL, p= 0.009).
12 months studies
Studies HZC102970 and HZC102871 were 52 week randomised, double-blind, parallel-group, studies comparing the efficacy and safety of FF/VI 200/25 micrograms, FF/VI 100/25 micrograms, FF/VI 50/25 micrograms and vilanterol 25 micrograms, all administered once daily. The primary endpoint was the reduction in the annual rate of moderate and severe exacerbations in subjects with COPD.
The results of both studies showed that treatment with FF/VI 100/25 micrograms once daily resulted in a 27% reduction in the annual rate of moderate or severe COPD exacerbations compared with vilanterol (95% CI 16, 37mL (p<0.001). Similar reductions in the time to first exacerbation and exacerbations requiring systemic corticosteroid use were observed with FF/VI 100/25 micrograms once daily.
In a pooled analysis of HZC102970 and HZC102871, at Week 52, the FF/VI 100/25 microgram group demonstrated greater improvement in trough FEV_1 compared with the vilanterol 25 microgram group (a difference of 42 mL in adjusted mean change from baseline;95% CI: 19, 64mL, p<0.001).
Non-clinical information
Pharmacological and toxicological effects seen with fluticasone furoate or vilanterol in nonclinical 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.
Carcinogenesis/mutagenesis
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.
Genetic toxicity studies indicate vilanterol does not represent a genotoxic hazard to humans. Consistent with findings for other beta$_2$-agonists, in lifetime inhalation studies vilanterol 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 Toxicology
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 was not teratogenic in rats. In inhalation studies in rabbits, vilanterol 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 had any adverse effects on fertility or pre- and post-natal development in rats.
PHARMACEUTICAL PARTICULARS
List of Excipients
Lactose monohydrate (which contains milk protein)
(12.5 milligram lactose monohydrate per blister)
Magnesium stearate
Incompatibilities
None
Shelf Life
The expiry date is indicated on the packaging.
In-use shelf-life
Following removal from the tray, the product may be stored for a maximum period of 1 month below 30°C
Special Precautions for Storage
Store below 30°C
If stored in a refrigerator allow the inhaler to return to room temperature for at least an hour before use.
Nature and Contents of Container
The plastic 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 desiccant packet. The tray is sealed with a peelable foil lid.
The inhaler contains two strips of 30 regularly distributed blisters, each containing a white powder.
Manufactured by:
Glaxo Operations UK Limited*,
Ware, Hertfordshire, UK
*member of the GSK group of companies.

Version number: GDS 04
Date of issue: 22 May 2014
THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
The doctor and the pharmacist are the experts in medicines, their benefits and risks.
Do not by yourself interrupt the period of treatment prescribed.
Do not repeat the same prescription without consulting your doctor.
Keep all medicaments out of the reach of children.
Council of Arab Health Ministers,
Union of Arab Pharmacists.

Instructions for Use/Handling
When you first use the Ellipta inhaler you do not need to check that it is working properly, and you do not need to prepare it for use in any special way. Just follow the instructions below.
The inhaler is packaged in a tray containing a desiccant packet, to reduce moisture. Throw this packet away — don't eat or inhale it.
When you take the inhaler out of the sealed tray, it will be in the 'closed' position. Don't open it until you are ready to inhale a dose of medicine.
The step- by-step instructions shown below for the 30-dose Ellipta inhaler also apply to the 7-dose Ellipta inhaler.
a) Read this before you start
If you open and close the cover without inhaling the medicine, you will lose the dose.
The lost dose will be securely held inside the inhaler, but it will no longer be available.
It is not possible to accidentally take extra medicine or a double dose in one inhalation.

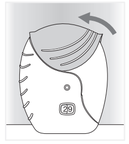
b) Prepare a dose
Wait to open the cover until you are ready to take your dose.
Do not shake the inhaler.
- Slide the cover fully down until you hear a "click".

Your medicine is now ready to be inhaled.
The dose counter counts down by 1 to confirm.
- If the dose counter does not count down as you hear the "click", the inhaler will not deliver medicine.
  Take it back to your pharmacist for advice.
- Do not shake the inhaler at any time.

c) Inhale your medication
- While holding the inhaler away from your mouth, breathe out as far as is comfortable.
  Don't breathe out into the inhaler.
- Put the mouthpiece between your lips, and close your lips firmly around it.
  Don't block the air vent with your fingers.

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

You may not be able to taste or feel the medicine, even when you are using the inhaler correctly.
d) Close the inhaler
If you want to clean the mouthpiece, use a dry tissue, before you close the cover.



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

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