



RELVAR ELLIPTA

Fluticasone furoate/vilanterol

1. NAME OF THE MEDICINAL PRODUCT

RELVAR ELLIPTA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-dispensed dose contains either 100/25 micrograms or 200/25 micrograms of fluticasone furoate/vilanterol (as trifenate).

Each single inhalation of fluticasone furoate/vilanterol provides a delivered dose of 92/22 micrograms of fluticasone furoate/vilanterol or 184/22 micrograms of fluticasone furoate/vilanterol.

3. PHARMACEUTICAL FORM

Inhalation powder

4. CLINICAL PARTICULARS

4.1. Indications

ASTHMA

RELVAR ELLIPTA is indicated for the maintenance treatment of asthma.

COPD

RELVAR ELLIPTA is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with an exacerbation history.

4.2. Dosage and Administration

RELVAR ELLIPTA is for inhalation only.

RELVAR ELLIPTA should be administered once daily either morning or evening but at the same time every day.

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

ASTHMA

Patients should be made aware that RELVAR ELLIPTA must be used regularly, even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta₂-agonist should be taken for immediate relief.

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.

Populations

Adults and adolescents aged 12 years and over

The recommended dose of RELVAR ELLIPTA is:

One inhalation of RELVAR ELLIPTA 100/25 micrograms once daily

or

One inhalation of RELVAR ELLIPTA 200/25 micrograms once daily

A starting dose of RELVAR ELLIPTA 100/25 micrograms should be considered for patients who require a low to mid dose of inhaled corticosteroid in combination with a long acting beta₂-agonist.

RELVAR ELLIPTA 200/25 micrograms should be considered for patients who require a higher dose of inhaled corticosteroid in combination with a long acting beta₂-agonist.

If patients are inadequately controlled on RELVAR ELLIPTA 100/25 micrograms, consider increasing the dose to 200/25 micrograms, which may provide additional improvement in asthma control.

Children

The safety and efficacy of RELVAR ELLIPTA has not been established in children less than 12 years of age.

COPD

Populations

Adults

The recommended dose of RELVAR ELLIPTA is:

One inhalation of RELVAR ELLIPTA 100/25 micrograms once daily.

RELVAR ELLIPTA 200/25 micrograms is not indicated for patients with COPD.

Children

The use in children is not relevant given the COPD indication for this product.

Special population: Asthma and COPD

Elderly

No dosage adjustment is required in patients over 65 years (see Pharmacokinetics – Special Patient Populations).

Renal impairment

No dose adjustment is required for patients with renal impairment (see Pharmacokinetics).

Hepatic Impairment

A clinical pharmacology study in subjects with mild, moderate and severe hepatic impairment showed up to 3-fold increase in systemic exposure to fluticasone furoate (AUC) (see Pharmacokinetics).

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 Pharmacokinetics).

4.3. 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.

4.4. 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. 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, 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 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 glaucoma and central serous chorioretinopathy (CSCR).

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.

Hyperglycaemia

There have been reports of increases in blood glucose levels with fluticasone furoate/vilanterol. This should be considered in patients with a history of, or with risk factors for, diabetes mellitus (see Adverse Reactions).

Pneumonia

An increase in pneumonia has been observed in patients with COPD receiving RELVAR ELLIPTA. 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 $<25 \text{ kg/m}^2$ and patients with a (forced expiratory volume) $\text{FEV}_1 < 50\%$ predicted. These factors should be considered when fluticasone furoate/vilanterol is prescribed and treatment should be re-evaluated if pneumonia occurs.

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 (see **Adverse Reactions**). No risk factors were identified.

4.5. 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 beta₂-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.

4.6. Pregnancy and Lactation

Fertility

There are no fertility data in humans. Animal studies showed no effect of vilanterol or fluticasone furoate on fertility (see Pre-Clinical Safety Data section).

Pregnancy

There has been limited pregnancy exposure in humans.

Animal studies have shown reproductive toxicity after administration of beta₂-agonists and corticosteroids (see Pre-Clinical Safety Data 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 beta₂-agonists are detected in human milk (see Pre-Clinical Safety Data 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.

4.7. Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of RELVAR ELLIPTA 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.

4.8. Adverse Reactions

Clinical trial data

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with RELVAR ELLIPTA. 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 reactions are listed by system organ class and frequency. The following convention has been used for the classification of adverse reactions:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1000$ to $< 1/100$.

Rare $\geq 1/10000$ 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 (see Warnings and Precautions)

In two replicate 12 month studies in a total of 3,255 patients with COPD (mean post-bronchodilator screening FEV₁ 45% of predicted, standard deviation (SD) 13%) 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 RELVAR ELLIPTA (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 RELVAR

ELLIPTA 200/25 micrograms, one during treatment with RELVAR ELLIPTA 100/25 micrograms and one post-treatment with vilanterol monotherapy.

In SUMMIT, a multi-centre, randomised study (HZC113782), 16,568 subjects received fluticasone furoate/vilanterol 100/25 micrograms, fluticasone furoate 100 micrograms, vilanterol 25 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 100/25 N=4,140	FF 100 N=4,157	VI 25 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 (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with RELVAR ELLIPTA 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.

**Cardiovascular events (see Warnings and Precautions)

For the SUMMIT study (see description above), cardiovascular adverse events are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 100/25 N=4,140	FF 100 N=4,157	VI 25 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 (see description above), fractures are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 100/25 N=4,140	FF 100 N=4,157	VI 25 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.

Post-marketing data

System organ class	Adverse reaction(s)	Frequency
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	Tremor	Rare
Cardiac disorders	Palpitations, Tachycardia	Rare Rare
Respiratory, thoracic and mediastinal disorders	Paradoxical bronchospasm	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Common

To report any side effect(s):

Kingdom of Saudi Arabia

-National Pharmacovigilance centre (NPC)

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

-GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: sa.aermi-saudi@gsk.com
- website: <https://healthksa.gsk.com/>
- P.O. Box 55850, Jeddah 21544, Saudi Arabia

4.9. Overdose

Symptoms and signs

There are no data available from clinical trials on overdose with RELVAR ELLIPTA.

An overdose of RELVAR ELLIPTA may produce signs and symptoms due to the individual components' actions, including those seen with overdose of other beta₂-agonists and consistent with the known inhaled corticosteroid class effects (see Warnings and Precautions).

Treatment

There is no specific treatment for an overdose with RELVAR ELLIPTA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Cardioselective beta-blockade should only be considered for profound vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

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.

5.2. Pharmacokinetics

Absorption

The absolute bioavailability for fluticasone furoate and vilanterol when administered by inhalation as RELVAR ELLIPTA 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 (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 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 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 (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

RELVAR ELLIPTA 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		
	RELVAR ELLIPTA 200/25OD* vs FF 200 OD	RELVAR ELLIPTA 100/25 OD vs FF 100 OD	RELVAR ELLIPTA 100/25 OD vs placebo OD	FF 100 OD vs placebo OD
Change from Baseline in Trough FEV ₁ (mL)				
Treatment difference (95% CI) p-value	193 (108, 277) p<0.001	36 (-48, 120) p=0.405	172 (87, 258) p<0.001	136 mL(51, 222) p=0.002
Weighted Mean Serial FEV ₁ over 0-24 hours post-dose (mL)				
Treatment difference (95% CI) p-value	136 (1, 270) p=0.048	116 (-5, 236) p=0.06	302 (178, 426) p<0.001	186 mL(62, 310) p=0.003
Change from Baseline in Rescue-free 24 hour periods				
Treatment difference (95% CI) p-value	11.7% (4.9, 18.4) p<0.001	10.6% (4.3, 16.8) p<0.001	9.3% (13.0, 25.6) p<0.001	8.7% (2.4, 15.0) 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 RELVAR ELLIPTA 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 RELVAR ELLIPTA 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 RELVAR ELLIPTA 100/25 group. The ratio of the exacerbation rate for RELVAR ELLIPTA 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 RELVAR ELLIPTA 100/25 compared with FF 100 (p=0.014). The 24-hour bronchodilator effect of RELVAR ELLIPTA was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). RELVAR ELLIPTA 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 (p<0.001 95% CI 52, 126mL at Endpoint). Forty four percent of patients in the RELVAR ELLIPTA 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)-two one-year randomised controlled studies (HZC102970, HZC102871) , and one long-term study (SUMMIT) 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 RELVAR ELLIPTA 50/25 micrograms [n=206] and RELVAR ELLIPTA 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 RELVAR ELLIPTA 100/25 micrograms [n=204] and RELVAR ELLIPTA 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 FEV₁ from zero to 4 hours post-dose and change from baseline in pre-dose trough FEV₁ at the end of the study.

In an integrated analysis of both studies, RELVAR ELLIPTA 100/25 micrograms showed clinically meaningful improvements in lung function. At the 24-week time point RELVAR ELLIPTA 100/25 micrograms and vilanterol increased trough FEV₁ by 129 mL (95% CI 91, 167mL, p<0.001) and 83mL (95% CI 46, 121mL, p<0.001) respectively compared with placebo. RELVAR ELLIPTA 100/25 micrograms increased trough FEV₁ by 46ml compared with vilanterol (95% CI 8, 83mL, p= 0.017).

At the 24-week time point RELVAR ELLIPTA 100/25 micrograms and vilanterol had a higher weighted mean FEV₁ 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 FEV₁ over 0-4 hours between the fluticasone furoate/vilanterol 100/25 and vilanterol groups was 48 mL (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 RELVAR ELLIPTA 200/25 micrograms, RELVAR ELLIPTA 100/25 micrograms, fluticasone furoate/vilanterol 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 RELVAR ELLIPTA 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, 37% ($p \leq 0.001$)). Reductions in risk of time to first moderate or severe exacerbation and rate of exacerbations requiring corticosteroid use were also observed with fluticasone furoate/vilanterol 100/25 micrograms once daily compared with vilanterol.

In a pooled analysis of HZC102970 and HZC102871, at Week 52, the RELVAR ELLIPTA 100/25 microgram group demonstrated greater improvement in trough FEV₁ compared with the vilanterol 25 microgram group (a difference of 42 mL in adjusted mean change from baseline; 95% CI: 19, 64 mL, $p < 0.001$).

Long-term study

SUMMIT was a multi-centre, randomised, double-blind study evaluating the effect on survival of RELVAR ELLIPTA 100/25 micrograms compared with placebo in 16,568 subjects. Subjects were treated for up to 4 years (mean 1.7 years) with either RELVAR ELLIPTA 100/25 micrograms, fluticasone furoate 100 micrograms, vilanterol 25 micrograms, or placebo. All subjects had COPD with moderate airflow limitation ($\geq 50\%$ and $\leq 70\%$ predicted FEV₁) and a history of, or an increased risk of, cardiovascular disease.

Survival with RELVAR ELLIPTA was not significantly improved compared with placebo (HR 0.878; 95% CI: 0.739, 1.042; $p = 0.137$), FF (HR 0.964; 95% CI: 0.808, 1.149; $p = 0.681$) or VI (HR 0.912; 95% CI: 0.767, 1.085; $p = 0.299$). All-cause mortality was: fluticasone furoate/vilanterol, 6.0%; placebo, 6.7%; fluticasone furoate, 6.1%; vilanterol, 6.4%).

RELVAR ELLIPTA slowed the rate of decline in lung function as measured by FEV₁, by 8 mL/year compared with placebo (95% CI: 1, 15; $p = 0.019$). There was no impact (0 mL/year; 95% CI: -6, 7; $p = 0.913$) on the rate of decline for RELVAR ELLIPTA compared with fluticasone furoate; there was a difference of 10 mL/year for RELVAR ELLIPTA compared with vilanterol (95% CI: 3, 16; $p = 0.004$). The mean rate of decline in FEV₁ was: RELVAR ELLIPTA, 38 mL/year; placebo, 46 mL/year; fluticasone furoate, 38 mL/year; vilanterol, 47 mL/year.

The risk of a cardiovascular composite event (on-treatment cardiovascular death, myocardial infarction, stroke, unstable angina, or transient ischemic attack) with RELVAR ELLIPTA was not significantly lower than placebo (HR 0.926; 95% CI: 0.750, 1.143; $p = 0.475$), FF (HR 1.033; 95% CI: 0.834, 1.281; $p = 0.763$) or VI (HR 0.938; 95% CI: 0.761, 1.155; $p = 0.545$). The incidence of cardiovascular composite events was: RELVAR ELLIPTA, 4.2%; placebo, 4.2%; fluticasone furoate, 3.9%; vilanterol 4.4%.

RELVAR ELLIPTA demonstrated a larger mean change from baseline in post-bronchodilator FEV₁ at Day 360 compared with placebo (89 mL; 95% CI: 76, 102; $p < 0.001$), FF (40 mL; 95% CI: 27, 53; $p < 0.001$), and VI (26 mL; 95% CI: 13, 39;

p<0.001). The adjusted mean change from baseline was: RELVAR ELLIPTA 50 mL, placebo, -39 mL; fluticasone furoate, 9 mL; vilanterol, 24 mL.

RELVAR ELLIPTA reduced the annual rate of moderate or severe exacerbations by 29% (95% CI: 22, 35; p<0.001) compared with placebo, by 19% compared with FF (95% CI: 12, 26; p<0.001) and by 21% compared with VI (95% CI: 14, 28; p<0.001). The annual rate of moderate or severe exacerbations was 0.25 for RELVAR ELLIPTA, 0.35 for placebo, 0.31 for fluticasone furoate, and 0.31 for vilanterol.

RELVAR ELLIPTA reduced the annual rate of severe exacerbations (i.e. requiring hospitalisation) by 27% (95% CI: 13, 39; p<0.001) compared with placebo, by 11% compared with FF (95% CI: -6, 25; p=0.204) and by 9% compared with VI (95% CI: -8, 24; p=0.282). The annual rate of exacerbations requiring hospitalisation was 0.05 for RELVAR ELLIPTA, 0.07 for placebo, 0.06 for fluticasone furoate, and 0.06 for vilanterol.

5.3. Pre-clinical 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.

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 beta₂-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 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 had any adverse effects on fertility or pre- and post-natal development in rats.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Lactose monohydrate (which contains milk protein)
(12.5 milligram lactose monohydrate per blister)

Magnesium stearate

6.2. Incompatibilities

None

6.3. 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

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.

6.4. Special Precautions for Storage

Storage condition depends on local registration requirements.

Store below 30°C

If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

6.5. Nature and Contents of Container

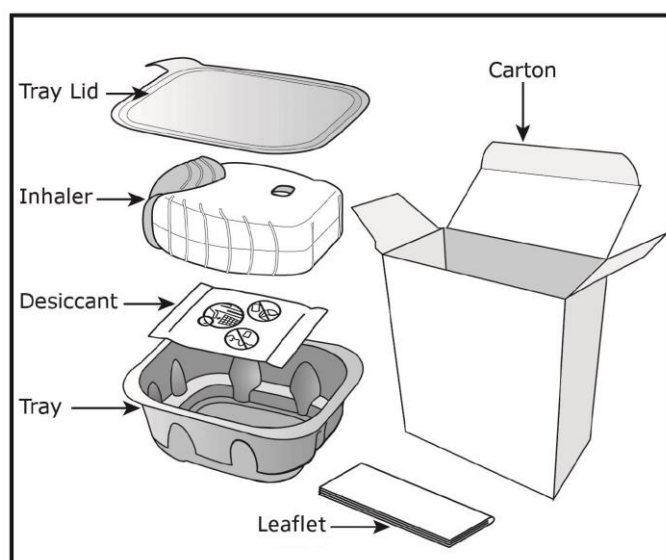
The plastic Ellipta inhaler consists of a light grey body, a pale blue or yellow mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant **sachet**. The tray is sealed with a peelable foil lid.

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

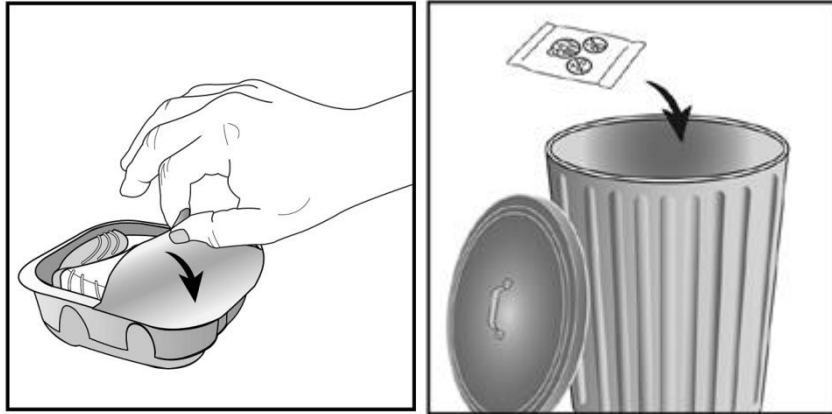
6.6. Instructions for Use/Handling

When you first use the Ellipta inhaler you do not need to check that it is working properly. It is ready for use straightaway, and you do not need to prepare it for use in any special way. Just follow these step-by-step instructions.

Your Ellipta inhaler carton contains



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



When you take the inhaler out of its box, it will be in the ‘closed’ position. **Don’t open the inhaler** until you are ready to inhale a dose of medicine. Write the “Discard by” date on the inhaler label in the space provided.

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

a) Read this before you start

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

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

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

Dose counter

This shows how many doses of medicine are left in the inhaler.

Before the inhaler has been used, it shows exactly 30 doses.

It counts down by **1** each time you open the cover.

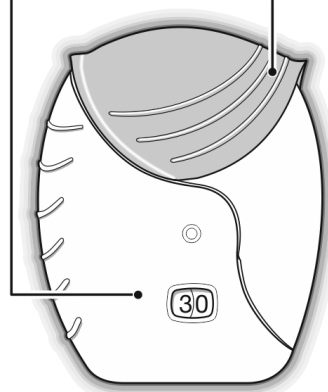
When fewer than 10 doses are left, half of the dose counter shows red.

After you have used the last dose, **half of the dose counter shows red and the number 0 is displayed.** Your inhaler is now empty.

If you open the cover after this, the dose counter will change from half red to completely red.

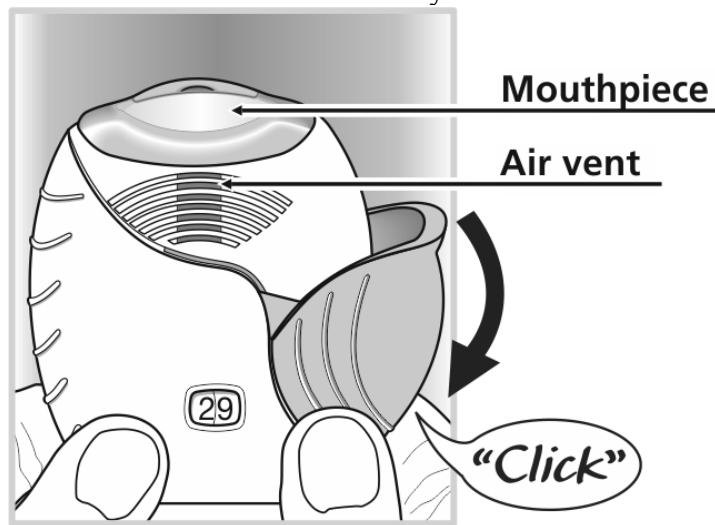
Cover

Each time you open this, you prepare one dose of medicine.



b) Prepare a dose

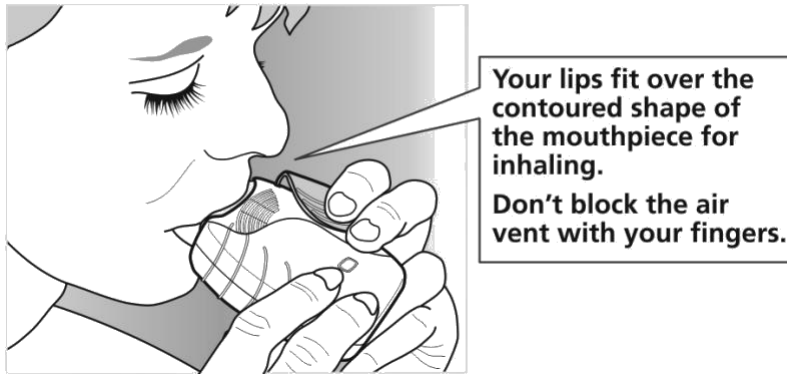
- Wait to open the cover until you are ready to take your dose.
- Do not shake the inhaler.
- Slide the cover down until you hear a “click”.



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

c) Inhale your medication

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



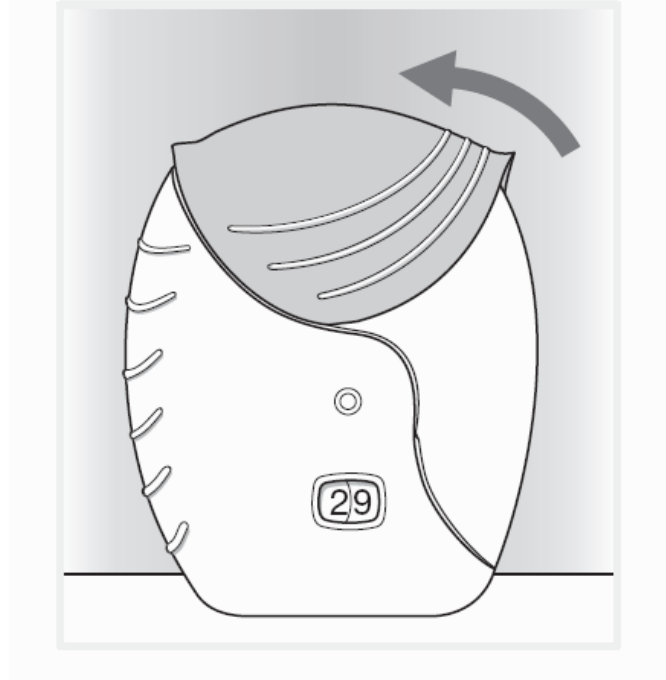
- Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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

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

(d) Close the inhaler and rinse your mouth

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



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

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

Not all presentations are available in every country.

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