RELVAR ELLIPTA

Fluticasone furoate/vilanterol

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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.

Fluticasone furoate/vilanterol has been formulated in two strengths and two pack sizes, delivering either 14 or 30 inhalations per Ellipta inhaler.

CLINICAL INFORMATION

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

- patients already adequately controlled on both inhaled corticosteroid and long-acting $beta_2$-agonist

COPD

RELVAR ELLIPTA 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

Pharmaceutical form: Inhalation powder.

RELVAR ELLIPTA is for inhalation only.

RELVAR ELLIPTA should be administered once daily either morning or evening but at the same time every day. If a dose is missed, the next dose should be taken at the usual time the next 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 beta$_2$-agonist should be taken for immediate relief.

Patients should be regularly reassessed by a healthcare professional so that the strength of *RELVAR ELLIPTA* 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 beta$_2$-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 beta$_2$-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. 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.

Children

The use in children is not relevant for 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*).

Contraindications

RELVAR ELLIPTA is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to either *RELVAR ELLIPTA* 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*. In a placebo-controlled study in subjects with 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/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 Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract, glaucoma, central serous chorioretinopathy (CSCR)

and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

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.

Visual disturbance

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

Hyperglycaemia

There have been reports of increases in blood glucose levels 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 kg/m^2 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 common at the higher dose. 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.

Long-acting $beta_2$-adrenergic agonists

Long-acting $beta_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in *RELVAR ELLIPTA*, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol. Current available data are inadequate to

determine whether concurrent use of inhaled corticosteroids or other long-acting asthma control drugs mitigates the increased risk of asthma-related death from LABA.

Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

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 CYP3A4 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 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 (400 mg). Co-administration increased mean fluticasone furoate $AUC_{(0-24)}$ and C_{max} by 36% and 33% respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol $AUC_{(0-t)}$ and C_{max} 65% and 22% respectively. The increase in vilanterol

exposure was not associated with an increase in beta$_2$-agonist-related systemic effects on heart rate, blood potassium or QTcF interval.

Interaction with P-glycoprotein inhibitors

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

Sympathomimetic medicinal products

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

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 breastfeeding or to discontinue *RELVAR ELLIPTA* therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *RELVAR ELLIPTA* on driving performance nor 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 *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.

The most commonly reported adverse reactions with fluticasone furoate and vilanterol were headache and nasopharyngitis.

With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently observed in patients with COPD.

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: ≥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
Eye disorders	Vision blurred	Uncommon
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 FEV_1 45% of predicted, standard deviation (SF) 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. 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 numbers 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 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 FEV_1 60% of predicted, SF 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 serious pneumonia events led to hospitalisation with either strength.

** 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
Respiratory, thoracic and mediastinal disorders	Paradoxical bronchospasm	Rare
Musculoskeletal and connective tissue disorders	Muscle spasms	Common

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 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 *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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

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 causes relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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.

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.

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. 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.

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 body weight (35 kg), vilanterol $AUC_{(0-24)}$ is predicted to be 35% higher than the population estimate (subject with COPD aged 60 years and body weight 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 <30 mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or $beta_2$-agonist systemic effects compared with healthy subjects. No dose adjustment is required for patients with renal impairment.

The effects of haemodialysis have not been studied.

Hepatic Impairment

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0–24)}$) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure (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 1,213 subjects with asthma (712 females) and 1,225 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 1,091 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 200/25 OD* vs FF 200 OD	*RELVAR ELLIPTA* 200/25 OD* Vs FP 500 BD	*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	210 (127, 294) p<0.001	36 (-48, 120) p=0.405	172 (87, 258) p<0.001	136 (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	206 (73, 339) p=0.003	116 (-5, 236) p=0.06	302 (178, 426) p<0.001	186 (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	6.3% (-0.4, 13.1) p=0.067	10.6% (4.3, 16.8) p<0.001	19.3% (13.0, 25.6) p<0.001	8.7% (2.4, 15.0) p=0.007
Change from Baseline in Percentage of Symptom-Free 24-hour Periods					
Treatment difference (95% CI) p-value	8.4% (2.0, 14.8) p=0.010	4.9% (-1.6, 11.3) p=0.137	12.1% (6.2, 18.1) p<0.001	18.0% (12.0, 23.9) p<0.001	5.8% (-0.1, 11.8) p=0.055
Change from Baseline in AM Peak Expiratory Flow					
Treatment difference (95% CI) p-value	33.5L/min (22.3, 41.7) p<0.001	32.9L/min (24.8, 41.1) p<0.001	14.6L/min (7.9, 21.3) p<0.001	33.3L/min (26.5, 40.0) p<0.001	18.7L/min (12.7, 25.4) p<0.001
Change from Baseline in PM Peak Expiratory Flow					
Treatment difference (95% CI) p-value	30.7L/min (22.5, 38.9) p<0.001	26.2L/min (18.0, 34.3) p<0.001	12.3L/min (5.8, 18.8) p<0.001	28.2L/min (21.7, 34.8) p<0.001	15.9 L/min (9.4, 22.5) p<0.001

*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] both administered once daily. 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).

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 FEV_1 at Weeks 12, 36 and 52 and Endpoint compared with FF 100 ($p<0.001$ 95% CI: 52, 126 mL 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).

Studies versus salmeterol/fluticasone propionate combinations

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

A randomised, double-blind, parallel group, 24-week study (201378) was conducted to demonstrate non-inferiority (using a margin of -100 mL for trough FEV_1) of fluticasone furoate/vilanterol 100/25 once daily to salmeterol/FP 50/250 twice daily in adults and adolescents whose asthma was well controlled following 4 weeks of treatment with open-label salmeterol/FP 50/250 twice daily (N=1,504). Subjects randomised to once-daily FF/VI maintained lung function comparable with those randomised to twice-daily salmeterol/FP [difference in trough FEV_1 of +19 mL (95% CI: -11, 49)].

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

Chronic Obstructive Pulmonary Disease

The efficacy of *RELVAR ELLIPTA* in the treatment of patients with COPD has been evaluated in two 6-month studies (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.

All patients were required to have a smoking history of at least 10 pack years; a post-salbutamol FEV_1/FVC ratio of less than or equal to 0.70; post-salbutamol FEV_1 less than or equal to 70% predicted and have a Modified Medica Research Council (mMRC) dyspnea score ≥ (scale 0-4) at screening. At screening, the mean pre-bronchodilator FEV_1 was 42.6% and 43.6% of predicted, and the mean reversibility was 15.9% and 12.0% in HZC112206 and HZC112207 respectively. 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, *RELVAR ELLIPTA* 100/25 micrograms showed clinically meaningful improvements in lung function. At Day 169, *RELVAR ELLIPTA* 100/25 micrograms and vilanterol increased trough FEV_1 by 129 mL (95% CI: 91, 167 mL, p<0.001) and 83 mL (95% CI: 46, 121 mL, p<0.001) respectively compared with placebo. *RELVAR ELLIPTA* 100/25 micrograms increased trough FEV_1 by 46 ml compared with vilanterol (95% CI: 8, 83 mL, p= 0.017).

At Day 168, *RELVAR ELLIPTA* 100/25 micrograms and vilanterol had a higher weighted mean FEV_1 over 0-4 hours of 193 mL (95% CI: 156, 230 mL, p<0.001) and 145 mL (95% CI: 108, 181 mL, p<0.001) respectively compared with placebo. The difference in weighted mean FEV_1 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-month studies

Studies HZC102970 and HZC102871 were 52-week randomised, double-blind, parallel-group, studies comparing the effect 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, on the annual rate of moderate/severe exacerbations in subjects with COPD with a smoking history of at least 10 pack years and a post-salbutamol FEV_1/FVC ratio less than or equal to 0.70 and post-salbutamol FEV_1 less than or equal to 70% predicted and documented history of ≥ 1 COPD exacerbation that required antibiotics and/or oral corticosteroids or hospitalisation in the 12 months prior to visit 1. The primary endpoint was the annual rate of moderate and severe exacerbations in subjects with COPD. Moderate/severe exacerbations were defined as worsening symptoms that required treatment with oral corticosteroids and/or antibiotics or in-patient hospitalisation. Both studies had a 4-week run-in during which all subjects received open-label salmeterol/FP 50/250 twice daily to standardise COPD pharmacotherapy and stabilise disease prior to randomisation to blinded study medication for 52 weeks. Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting bronchodilators (beta$_2$-agonist and anticholinergic), ipratropium/salbutamol combination products, oral beta$_2$-agonists, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment

of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of both studies showed that treatment with *RELVAR ELLIPTA* 100/25 micrograms once daily resulted in a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol (Table 2).

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

Endpoint	**HZC102970**		**HZC102871**		**HZC102970 and HZC102871 integrated**	
	Vilanterol (n=409)	*RELVAR ELLIPTA* 100/25 (n=403)	Vilanterol (n=409)	*RELVAR ELLIPTA* 100/25 (n=403)	Vilanterol (n=818)	*RELVAR ELLIPTA* 100/25 (n=806)
Moderate and severe exacerbations						
Adjusted mean annual rate	1.14	0.90	1.05	0.70	1.11	0.81
Ratio vs VI (95% CI) p-value % reduction (95% CI)		0.79 (0.64, 0.97) 0.024 21 (3, 36)		0.66 (0.54, 0.81) <0.001 34 (19, 46)		0.73 (0.63, 0.84) <0.001 27 (16, 37)
Absolute difference in number per year versus vilanterol (95% CI)		0.24 (0.03, 0.41)		0.36 (0.20, 0.48)		0.30 (0.18, 0.41)
Time to first exacerbation: Hazard ratio (95% CI) % risk reduction p-value		 0.80 (0.66, 0.99) 20 0.036		 0.72 (0.59, 0.89) 28 0.002		 0.76 (0.66, 0.88) 24 p<0.001

In an integrated analysis of HZC102970 and HZC102871 at Week 52, an improvement was seen when comparing the *RELVAR ELLIPTA* 100/25 micrograms versus vilanterol 25 microgram in adjusted mean trough FEV_1 (42 mL 95% CI: 19, 64 mL, p<0.001). The 24-hour bronchodilator effect of fluticasone furoate/vilanterol was maintained from the first dose through a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis).

Overall, across the two studies combined, 2,009 (62%) patients had cardiovascular history/risk factors at screening. The incidence of cardiovascular history/risk factors was similar across the treatment groups with patients most commonly suffering from hypertension (46%), followed by hypercholesterolemia (29%) and diabetes mellitus (12%). Similar effects in reduction of moderate and severe exacerbations were observed in this subgroup as compared with the overall population. In patients with a cardiovascular history/risk factors, *RELVAR ELLIPTA* 100/25 micrograms resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with vilanterol (adjusted mean annual rates of 0.83 and 1.18 respectively, 30% reduction (95% CI: 16, 42%, p<0.001)). Improvements were also seen in this subgroup at week 52 when comparing the *RELVAR ELLIPTA* 100/25 micrograms versus vilanterol 25 micrograms in adjusted mean trough FEV_1 (44 mL 95% CI: 15, 73 mL, p=0.003).

Long-term study

SUMMIT was a multi-centre, randomised, double-blind study evaluating the effects 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 (≥50% and ≤70% predicted FEV_1) and 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 FEV_1 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 FEV_1 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 ischaemic 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 FEV_1 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.

Studies versus salmeterol/fluticasone propionate combinations

In a 12-week study (HZA113107) in COPD patients both *RELVAR ELLIPTA* 100/25 micrograms given once daily in the morning and salmeterol/FP 50/500 micrograms given twice daily, demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV_1 of 130 mL (fluticasone furoate/vilanterol) and 108 mL (salmeterol/FP) demonstrated an overall improvement in lung function over 24 hours for both treatments. The adjusted mean treatment difference of 22 mL (95% CI: -18, 63 mL) between the groups was not statistically significant (p=0.282). The adjusted mean change from baseline in trough FEV_1 on Day 85 was 111 mL in the fluticasone furoate/vilanterol group and 88 mL in the salmeterol/FP group; the 23 mL (95% CI: -20, 66) difference between the treatment groups was not clinically meaningful or statistically significant (p=0.294). No comparative studies versus salmeterol or versus other established bronchodilators have been conducted to appropriately compare the effect on COPD exacerbations.

Non-Clinical Information

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

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 1.2- 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 INFORMATION

List of Excipients

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

Magnesium stearate

Shelf-Life

The expiry date is indicated on the packaging.

In-use shelf-life

The in-use shelf-life depends on the locally registered storage conditions (refer to the pack for information).

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.

Storage

The storage conditions depend on local registration requirements.

The storage conditions are detailed on the packaging.

If stored in the 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 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.

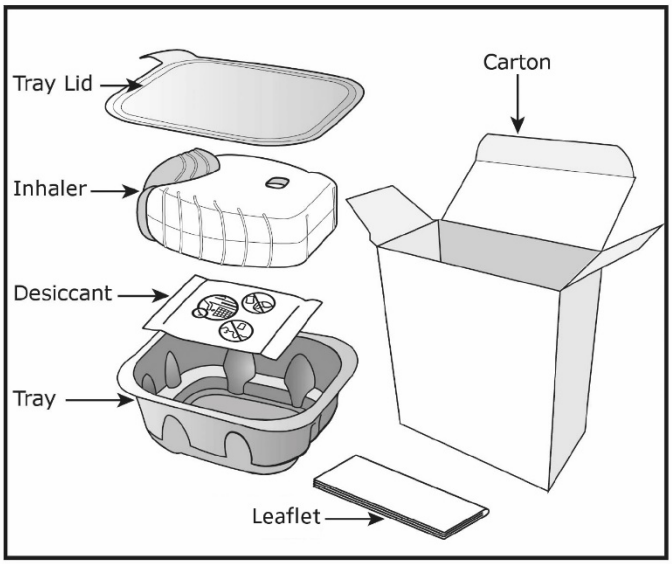
Incompatibilities

None

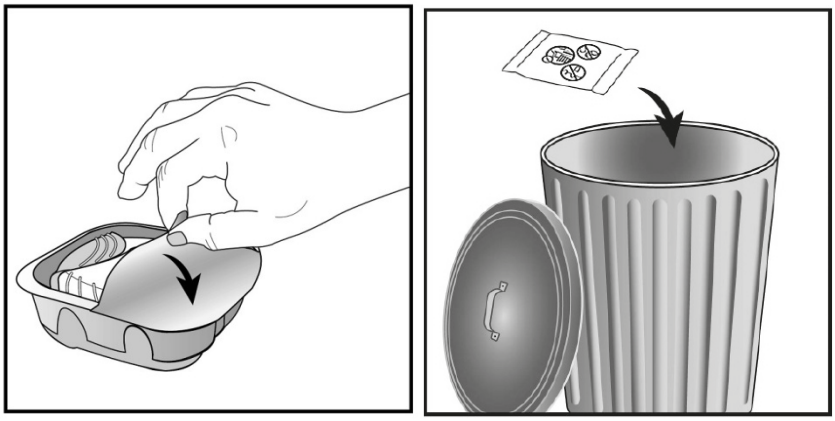
Use and Handling

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

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 — **do not** open, eat or inhale it.



When you take the inhaler out of its box, it will be in the 'closed' position. **Do not 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 "Discard by" date is 1 month from the date you first open the tray. **After this date, the inhaler should no longer be used.**

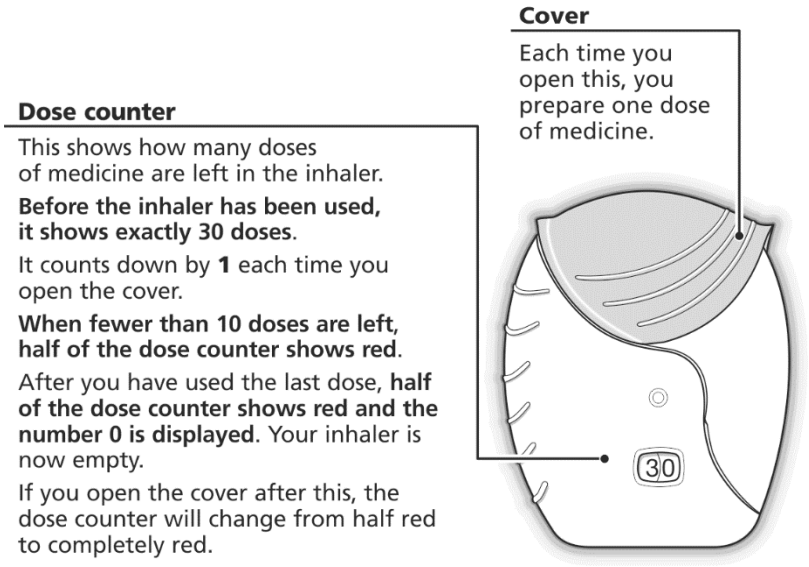
The step-by-step instructions shown below for the 30-dose (30-day supply) *Ellipta* inhaler also apply to the 14-dose *Ellipta* (14-day supply) inhaler.

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.

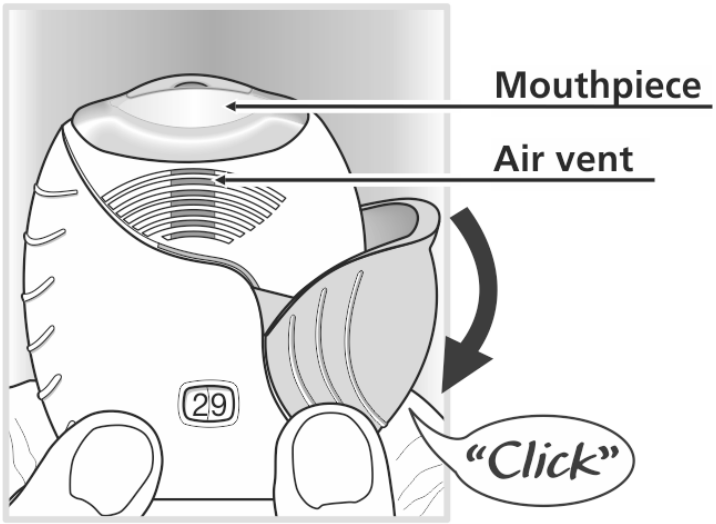


b) How to prepare a dose

Open the cover when 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.**

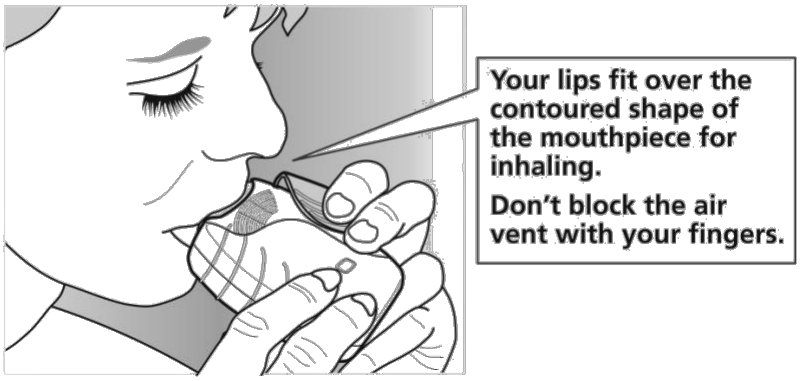
c) Inhale your medication

- **While holding the inhaler away from your mouth, breathe out as far as is comfortable.**

  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 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.**

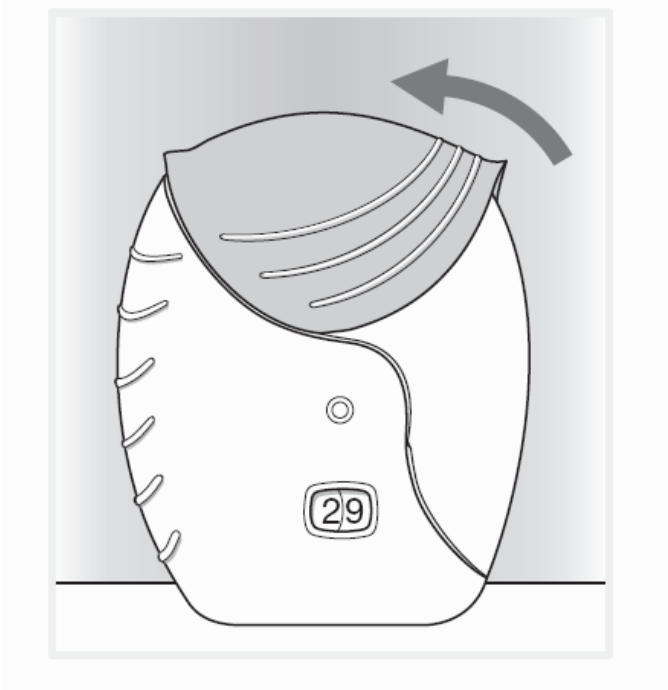
- **Breathe out slowly and gently.**

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 if possible

- **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.

Product Registrant:

GlaxoSmithKline Pte Ltd

23 Rochester Park

Singapore 139234

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[GSK logo]

[Innoviva logo]