

## 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 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.

## PHARMACEUTICAL FORM

Inhalation powder

## CLINICAL PARTICULARS

### Indications

#### ASTHMA

*RELVAR ELLIPTA* is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta<sub>2</sub>-agonist and inhaled corticosteroid) is appropriate:

- patients not adequately controlled with inhaled corticosteroids and “as needed” inhaled short-acting beta<sub>2</sub>-agonists.

#### COPD

*RELVAR ELLIPTA* is indicated for the symptomatic treatment of adults with COPD with a FEV<sub>1</sub><70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

### 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. 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<sub>2</sub>-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 beta<sub>2</sub>-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<sub>2</sub>-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 fluticasone furoate, vilanterol or any of the excipients.

## Warnings and Precautions

### Exacerbations

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

Patients should not stop therapy with *RELVAR ELLIPTA*, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with *RELVAR ELLIPTA*. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of *RELVAR ELLIPTA*.

### Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. *RELVAR ELLIPTA* should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

### Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic drugs, including *RELVAR ELLIPTA*. Therefore *RELVAR ELLIPTA* should be used with caution in patients with severe cardiovascular disease.

### Patients with hepatic impairment

For patients with moderate to severe hepatic impairment, the 100/25 micrograms dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions (see *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 and glaucoma 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.

### 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.

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. No risk factors were identified.

### Long-acting beta<sub>2</sub>-adrenergic agonists

Long-acting beta<sub>2</sub>-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 increase 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 chicken pox 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.

### Hyperglycaemia

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

## **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<sub>2</sub>-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 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<sub>(0-24)</sub> and C<sub>max</sub> 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<sub>(0-t)</sub> and C<sub>max</sub> 65% and 22% respectively. The increase in vilanterol exposure was not associated with an increase in beta<sub>2</sub>-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<sub>2</sub>-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 *Pre-clinical Safety Data section*).

### **Pregnancy**

There has been limited pregnancy exposure in humans.

Animal studies have shown reproductive toxicity after administration of beta<sub>2</sub>-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 beta<sub>2</sub>-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.

## **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.

## **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:  $\geq 1/10$

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

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

Rare:  $\geq 1/10000$  to  $< 1/1000$

Very rare:  $< 1/10000$

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

**Description of selected adverse reactions**

**\*Pneumonia**

In two replicate 12-month studies in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the fluticasone furoate (at strengths of 50, 100, and 200 micrograms)/vilanterol 25 micrograms combination than in those receiving vilanterol 25 micrograms alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving *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. Risk factors for pneumonia with fluticasone furoate/vilanterol observed in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m<sup>2</sup> and patients with an FEV<sub>1</sub><50% predicted (see *Warnings and Precautions*).

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with *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.

### \*\*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.

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         |
| Psychiatric disorders    | Anxiety  | Rare         |
| Nervous system disorders | Tremor   | Rare         |
| Cardiac disorders        | Palpitations,<br>Tachycardia   | Rare<br>Rare |

## 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<sub>2</sub>-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<sub>2</sub>-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, beta<sub>2</sub>-adrenergic agonist (LABA).

The pharmacologic effects of beta<sub>2</sub>-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.

## 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<sub>1</sub>- and β<sub>2</sub>-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<sub>(0-24)</sub> 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<sub>(0-24)</sub> is predicted to be 35% higher than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg), whilst C<sub>max</sub> 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<sub>2</sub>-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<sub>(0-24)</sub>) 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<sub>max</sub> 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:

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Summary of Data from Studies HZA106829 and HZA106827

| Study No.  | HZA106829                                    |  | HZA106827                                    |   |                                   |
|--|--|--|--|---|-----------------------------------|
|  | <i>RELVAR ELLIPTA</i> 200/25OD* vs FF 200 OD | <i>RELVAR ELLIPTA</i> 200/25OD* Vs FP 500 BD | <i>RELVAR ELLIPTA</i> 100/25 OD vs FF 100 OD | <i>RELVAR ELLIPTA</i> 100/25 OD vs placebo OD | FF 100 OD vs placebo OD           |
| Change from Baseline in Trough FEV <sub>1</sub> (mL)                 |  |  |  |   |                                   |
| Treatment difference (95% CI)<br>p-value                             | 193 (108, 277)<br>p<0.001                    | 210 (127, 294)<br>p<0.001                    | 36 (-48, 120)<br>p=0.405                     | 172 (87, 258)<br>p<0.001                      | 136 mL(51, 222)<br>p=0.002        |
| Weighted Mean Serial FEV <sub>1</sub> over 0-24 hours post-dose (mL) |  |  |  |   |                                   |
| Treatment difference (95% CI)<br>p-value                             | 136 (1, 270)<br>p=0.048                      | 206 (73, 339)<br>p=0.003                     | 116 (-5, 236)<br>p=0.06                      | 302 (178, 426)<br>p<0.001                     | 186 mL(62, 310)<br>p=0.003        |
| Change from Baseline in Rescue-free 24 hour periods                  |  |  |  |   |                                   |
| Treatment difference (95% CI)<br>p-value                             | 11.7% (4.9, 18.4)<br>p<0.001                 | 6.3% (-0.4, 13.1)<br>p=0.067                 | 10.6% (4.3, 16.8)<br>p<0.001                 | 19.3% (13.0, 25.6)<br>p<0.001                 | 8.7% (2.4, 15.0)<br>p=0.007       |
| Change from Baseline in Percentage of Symptom-Free 24-hour Periods   |  |  |  |   |                                   |
| Treatment difference (95% CI)<br>p-value                             | 8.4% (2.0, 14.8)<br>p=0.010                  | 4.9% (-1.6, 11.3)<br>p=0.137                 | 12.1% (6.2, 18.1)<br>p<0.001                 | 18.0% (12.0, 23.9)<br>p<0.001                 | 5.8% (-0.1, 11.8)<br>p=0.055      |
| Change from Baseline in AM Peak Expiratory Flow                      |  |  |  |   |                                   |
| Treatment difference (95% CI)<br>p-value                             | 33.5L/min (22.3, 41.7)<br>p<0.001            | 32.9L/min (24.8, 41.1)<br>p<0.001            | 14.6L/min (7.9, 21.3)<br>p<0.001             | 33.3L/min (26.5, 40.0)<br>p<0.001             | 18.7L/min (12.7, 25.4)<br>p<0.001 |
| Change from Baseline in PM Peak Expiratory Flow                      |  |  |  |   |                                   |
| Treatment difference (95% CI)<br>p-value                             | 30.7L/min (22.5, 38.9)<br>p<0.001            | 26.2L/min (18.0, 34.3)<br>p<0.001            | 12.3L/min (5.8, 18.8)<br>p<0.001             | 28.2L/min (21.7, 34.8)<br>p<0.001             | 15.9 L/min (9.4, 22.5)<br>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<sub>1</sub> 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  $\leq 0.75$ ) 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 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<sub>1</sub> 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<sub>1</sub> 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 ( $p=0.485$ ).

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 fluticasone furoate and vilanterol in the treatment of patients with COPD has been evaluated in two 6-month (HZA112206, HZA112207) and two one-year randomised controlled studies (HZA102970, HZA102871) in patients with a clinical diagnosis of COPD.

#### Six-month studies

HZA112206 and HZA112207 were 24 week randomised, double-blind, placebo controlled, parallel group studies comparing the effect of the combination to vilanterol and FF alone and placebo. HZA112206 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.

HZA112207 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<sub>1</sub>/FVC ratio of less than or equal to 0.70; post-salbutamol FEV<sub>1</sub> less than

or equal to 70% predicted and have a Modified Medica Research Council (mMRC) dyspnea score  $\geq$  (scale 0-4) at screening. At screening, the mean pre-bronchodilator FEV<sub>1</sub> 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<sub>1</sub> from zero to 4 hours post-dose and change from baseline in pre-dose trough FEV<sub>1</sub> 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<sub>1</sub> by 129 mL (95% CI 91, 167 mL, p<0.001) and 83mL (95% CI 46, 121mL, p<0.001) respectively compared with placebo. *RELVAR ELLIPTA* 100/25 micrograms increased trough FEV<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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 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<sub>1</sub>/FVC ratio less than or equal to 0.70 and post-salbutamol FEV<sub>1</sub> less than or equal to 70% predicted and documented history of  $\geq$  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<sub>2</sub>-agonist and anticholinergic), ipratropium/salbutamol combination products, oral beta<sub>2</sub>-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) | <i>RELVAR ELLIPTA</i> 100/25 (n=403) | Vilanterol (n=409) | <i>RELVAR ELLIPTA</i> 100/25 (n=403) | Vilanterol (n=818)                 | <i>RELVAR ELLIPTA</i> 100/25 (n=806) |
| <b>Moderate and severe exacerbations</b>                             |                    |                                      |                    |                                      |                                    |                                      |
| Adjusted mean annual rate  | 1.14               | 0.90                                 | 1.05               | 0.70                                 | 1.11                               | 0.81                                 |
| Ratio vs VI<br>95% CI  |                    | 0.79<br>(0.64, 0.97)                 |                    | 0.66<br>(0.54, 0.81)                 |                                    | 0.73<br>(0.63, 0.84)                 |
| p-value  |                    | 0.024                                |                    | <0.001                               |                                    | <0.001                               |
| % reduction<br>(95% CI)  |                    | 21<br>(3, 36)                        |                    | 34<br>(19, 46)                       |                                    | 27<br>(16, 37)                       |
| Absolute difference in number per year versus vilanterol<br>(95% CI) |                    | 0.24<br>(0.03, 0.41)                 |                    | 0.36<br>(0.20, 0.48)                 |                                    | 0.30<br>(0.18, 0.41)                 |
| Time to first exacerbation:<br><br>Hazard ratio<br>(95% CI)          |                    | 0.80<br>(0.66, 0.99)                 |                    | 0.72<br>(0.59, 0.89)                 |                                    | 0.76<br>(0.66, 0.88)                 |
| % risk reduction   |                    | 20                                   |                    | 28                                   |                                    | 24                                   |
| p-value  |                    | 0.036                                |                    | 0.002                                |                                    | 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<sub>1</sub> ( 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 2009 (62%) patients had cardiovascular history/risk factors at screening. The incidence of cardiovascular history/risk factors was similar across the treatment groups with patients most commonly suffering from hypertension (46%), followed by hypercholesterolemia (29%) and diabetes mellitus (12%). Similar effects in reduction of moderate and severe exacerbations were observed in this subgroup as compared with the overall population. In patients with a cardiovascular history/risk factors, *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<sub>1</sub> (44 mL 95% CI: 15, 73 mL, ( $p = 0.003$ )).

#### 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<sub>1</sub> 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<sub>1</sub> 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.

### **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 beta<sub>2</sub>-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<sub>2</sub>-agonists, in lifetime inhalation studies

vilanterol caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

## **Reproductive Toxicology**

Effects seen following inhalation administration of fluticasone furoate in combination with vilanterol in rats were similar to those seen with fluticasone furoate alone.

Fluticasone furoate was not teratogenic in rats or rabbits, but delayed development in rats and caused abortion in rabbits at maternally toxic doses. There were no effects on development in rats at exposures approximately 3-times greater than those at the maximum recommended human dose, based on AUC.

Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, vilanterol caused effects similar to those seen with other beta<sub>2</sub>-agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 84-times greater than those at the maximum recommended human dose, based on AUC.

Neither fluticasone furoate nor vilanterol had any adverse effects on fertility or pre- and post-natal development in rats.

## **PHARMACEUTICAL PARTICULARS**

### **List of Excipients**

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

Magnesium stearate

### **Incompatibilities**

None

### **Shelf-Life**

The expiry date is indicated on the packaging.

### **In-use shelf-life**

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

### **Special Precautions for Storage**

Storage condition depends on local registration requirements.

Store below 30°C

### **Nature and Contents of Container**

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

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

### **Instructions for Use/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.

The inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. Throw this sachet away — do not eat or inhale it.

When you take the inhaler out of its box, it will be in the ‘closed’ position. Do not open it until you are ready to inhale a dose of medicine.

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

a) Read this before you start

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

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

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

**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.

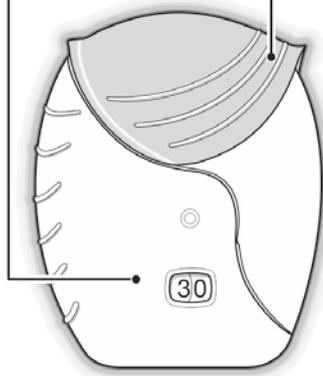
**When fewer than 10 doses are left, half of the dose counter shows red.**

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.

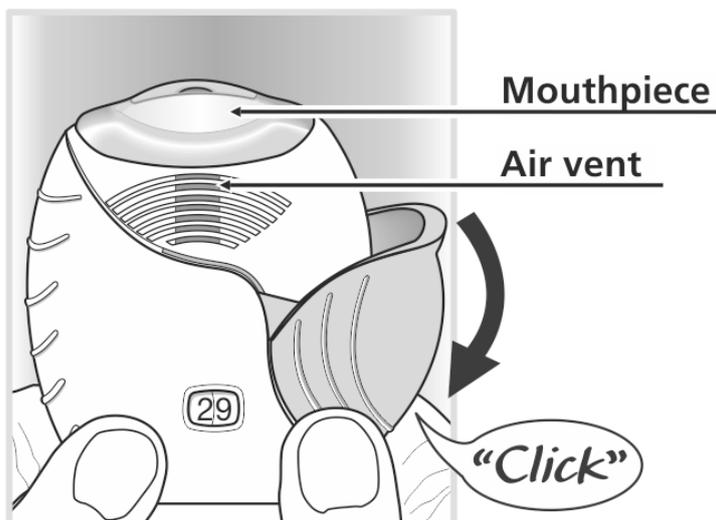


b) How to prepare a dose

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.



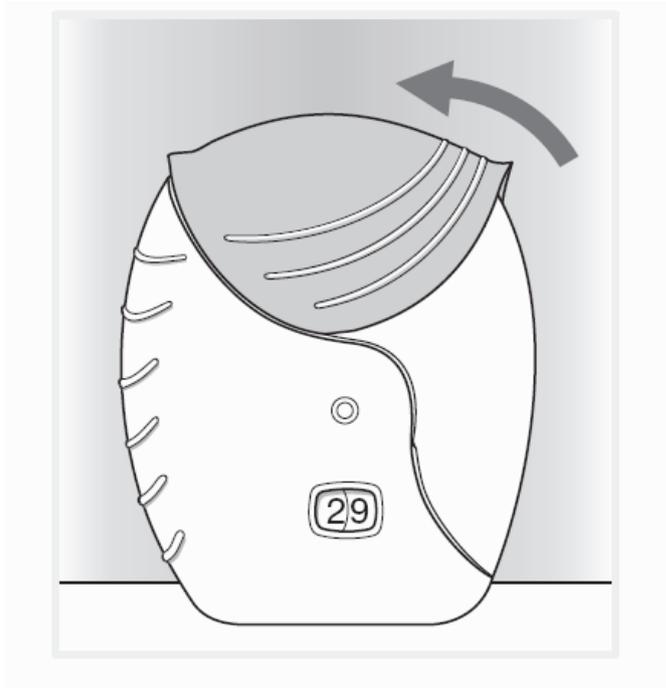
- Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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

(d) Close the inhaler and rinse your mouth if possible

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

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



- 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.

Manufactured by:

Glaxo Operations UK Limited\*,  
Ware,

Hertfordshire,  
UK

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