

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate). This corresponds to a pre-dispensed dose of 100 micrograms of fluticasone furoate and 25 micrograms vilanterol (as trifenate).

Excipients with known effect:

Each delivered dose contains approximately 25 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed
(Inhalation powder).

White powder in a light grey inhaler with a yellow mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Relvar Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonist and inhaled corticosteroid) is appropriate:

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

COPD (Chronic Obstructive Pulmonary Disease)

Relvar Ellipta is indicated for the symptomatic treatment of adults with COPD with a FEV₁ < 70% predicted normal (post-bronchodilator) with an exacerbation history despite regular bronchodilator therapy.

4.2 Posology and method of administration

Posology

Asthma

Adults and adolescents aged 12 years and over

One inhalation of Relvar Ellipta 92/22 micrograms once daily.

Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic.

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

A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta₂-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.

Patients should be regularly reassessed by a healthcare professional so that the strength of fluticasone furoate/vilanterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Relvar Ellipta 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting beta₂-agonist.

Patients with asthma should be given the strength of Relvar Ellipta containing the appropriate fluticasone furoate (FF) dosage for the severity of their disease. Prescribers should be aware that in patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily, while FF 200 micrograms once daily is approximately equivalent to FP 500 micrograms twice daily.

Children aged under 12 years

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

COPD

Adults aged 18 years and over

One inhalation of Relvar Ellipta 92/22 micrograms once daily.

Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions (see sections 4.4 and 4.8).

Patients usually experience an improvement in lung function within 16-17 minutes of inhaling Relvar Ellipta.

Paediatric population

There is no relevant use of Relvar Ellipta in the paediatric population for the indication of COPD.

Special populations

Elderly patients (>65 years)

No dose adjustment is required in this population (see section 5.2).

Renal impairment

No dose adjustment is required in this population (see section 5.2).

Hepatic impairment

Studies in subjects with mild, moderate and severe hepatic impairment showed an increase in systemic exposure to fluticasone furoate (both C_{max} and AUC) (see section 5.2).

Caution should be exercised when dosing patients with hepatic impairment who may be more at risk of systemic adverse reactions associated with corticosteroids.

For patients with moderate or severe hepatic impairment the maximum dose is 92/22 micrograms (see section 4.4).

Method of administration

Relvar Ellipta is for inhalation use only.

It should be administered at the same time of the day, each day.

The final decision on evening or morning dosing should be left to the discretion of the physician.

If a dose is missed the next dose should be taken at the usual time the next day.

If stored in a refrigerator, the inhaler should be allowed to return to room temperature for at least an hour before use.

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

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

The Ellipta inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. Once opened the desiccant sachet should be discarded.

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

When the inhaler is taken out of its tray, it will be in the 'closed' position. The "Discard by" date should be written on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date of opening the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

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

Instructions for use

1. Read this before you start

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

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

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.

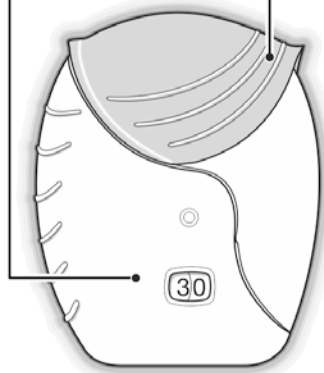
When fewer than 10 doses are left, half of the dose counter shows red.

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.



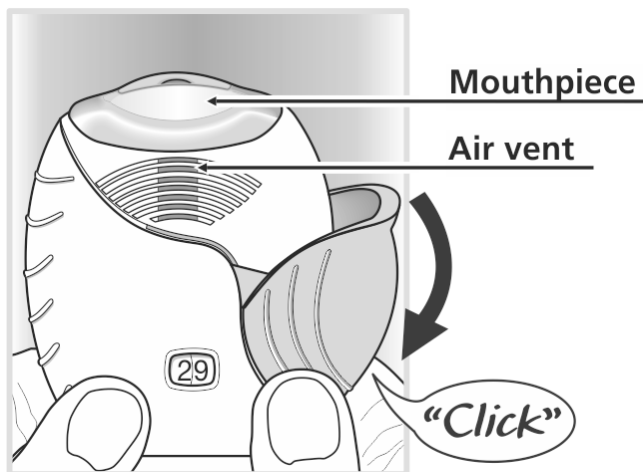
2. How to prepare a dose

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

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

The medicine is now ready to be inhaled. The dose counter counts down by 1 to confirm.

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



3. How to inhale the medicine

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

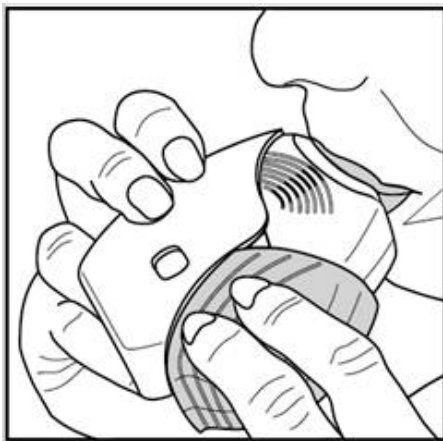
Do not breathe out into the inhaler.

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

Do not block the air-vents with your fingers.

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

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



Your lips fit over the contoured shape of the mouthpiece for inhaling.

Do not block the air vent with your fingers.

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

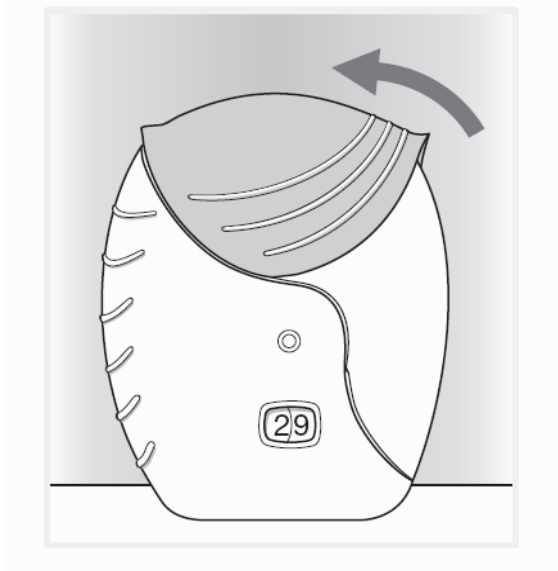
4. Close the inhaler and rinse your mouth

If you want to clean the mouthpiece, use a **dry tissue**, **before** closing 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 to develop a sore mouth or throat as side effects.



4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms 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 fluticasone furoate/vilanterol in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with fluticasone furoate/vilanterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with Relvar Ellipta.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. Relvar Ellipta should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including Relvar Ellipta. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Patients with hepatic impairment

For patients with moderate to severe hepatic impairment, the 92/22 micrograms dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions (see section 5.2).

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Fluticasone furoate/vilanterol should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Hyperglycaemia

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

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of systemic corticosteroid-related adverse reactions (see section 4.8).

Pneumonia in patients with asthma

The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Clinically significant drug interactions mediated by fluticasone furoate/vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

Beta₂-adrenergic blockers may weaken or antagonise the effect of beta₂-adrenergic agonists. Concurrent use of both non-selective and selective beta₂-adrenergic blockers should be avoided unless there are compelling reasons for their use.

Interaction with CYP3A4 inhibitors

Fluticasone furoate and vilanterol are both rapidly cleared by extensive first pass metabolism mediated by the liver enzyme CYP3A4.

Caution is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, and concomitant use should be avoided. A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (184/22 micrograms) and the strong CYP3A4 inhibitor ketoconazole (400mg). Co-administration increased mean fluticasone furoate AUC₍₀₋₂₄₎ and C_{max} by 36% and 33%, respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol AUC_(0-t) and C_{max} 65% and 22%, respectively. The increase in vilanterol exposure was not associated with an increase in beta₂-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Interaction with P-glycoprotein inhibitors

Fluticasone furoate and vilanterol are both substrates of P-glycoprotein (P-gp). A clinical pharmacology study in healthy subjects with co-administered vilanterol and the potent P-gp and moderate CYP3A4

inhibitor verapamil did not show any significant effect on the pharmacokinetics of vilanterol. Clinical pharmacology studies with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

Sympathomimetic medicinal products

Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) may potentiate the adverse reactions of fluticasone furoate/vilanterol. Relvar Ellipta should not be used in conjunction with other long-acting beta₂-adrenergic agonists or medicinal products containing long-acting beta₂-adrenergic agonists.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant (see section 5.3). There are no or limited data from the use of fluticasone furoate and vilanterol trifenate in pregnant women.

Administration of fluticasone furoate/vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding

There is insufficient information on the excretion of fluticasone furoate or vilanterol trifenate and/or metabolites in human milk. However, other corticosteroids and beta₂-agonists are detected in human milk (see section 5.3). A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue fluticasone furoate/vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no effect of fluticasone furoate/vilanterol trifenate on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Fluticasone furoate or vilanterol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with fluticasone furoate/vilanterol. In the asthma clinical development program a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development programme a total of 6,237 subjects were included in an integrated assessment of adverse reactions.

The most commonly reported adverse reactions with fluticasone furoate and vilanterol were headache and nasopharyngitis. With the exception of pneumonia and fractures, the safety profile was similar in patients

with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class and frequency. The following convention has been used for the classification of frequencies: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| System organ class | Adverse reaction(s) | Frequency |
|--|---|--------------------------|
| Infections and infestations | Pneumonia* Upper respiratory tract infection Bronchitis Influenza Candidiasis of mouth and throat | Common |
| Immune system disorders | Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. | Rare |
| Nervous system disorders | Headache Tremor | Very common Rare |
| Psychiatric disorders | Anxiety | Rare |
| Cardiac disorders | Extrasystoles Palpitations Tachycardia | Uncommon Rare Rare |
| Respiratory, thoracic and mediastinal disorders | Nasopharyngitis Oropharyngeal pain Sinusitis Pharyngitis Rhinitis Cough Dysphonia | Very common Common |
| Gastrointestinal disorders | Abdominal pain | Common |
| Musculoskeletal and connective tissue disorders | Arthralgia Back pain Fractures** Muscle spasms | Common |
| General disorders and administration site conditions | Pyrexia | Common |

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

Description of selected adverse reactions

Pneumonia

In an integrated analysis of the two replicate one year studies in COPD with an exacerbation in the preceding year (n = 3255), the number of pneumonia events per 1000 patient years was 97.9 with FF/VI 184/22, 85.7 in the FF/VI 92/22 and 42.3 in the VI 22 group. For severe pneumonia the corresponding number of events per 1000 patient years were 33.6, 35.5, and 7.6 respectively, while for serious pneumonia the corresponding events per 1000 patient years were 35.1 for FF/VI 184/22, 42.9 with FF/VI 92/22, 12.1 with VI 22. Finally, the exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 184/22 versus 1.5 for FF/VI 92/22 and 0 for VI 22.

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia per 1000 patient years was 18.4 for FF/VI 184/22 versus 9.6 for FF/VI 92/22 and 8.0 in the placebo group.

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 22 micrograms group (<1%). Although there were more fractures in the Relvar Ellipta groups compared with the vilanterol 22 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms and signs

An overdose of fluticasone furoate/vilanterol may produce signs and symptoms due to the individual component's actions, including those seen with overdose of other beta₂-agonists and consistent with the known inhaled corticosteroid class effects (see section 4.4).

Treatment

There is no specific treatment for an overdose with fluticasone furoate/vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Cardioselective beta-blockade should only be considered for profound vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking medicinal products should be used with caution in patients with a history of bronchospasm.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, Adrenergics and other drugs for obstructive airway diseases, ATC code: R03AK10.

Mechanism of action

Fluticasone furoate and vilanterol represent two classes of medications (a synthetic corticosteroid and a selective, long-acting beta₂-receptor agonist).

Pharmacodynamic effects

Fluticasone furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects asthma and COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines involved in inflammation).

Vilanterol trifenate

Vilanterol trifenate is a selective long-acting, beta₂-adrenergic agonist (LABA). The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including vilanterol trifenate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the beta₂-receptor gene, increasing receptor number and sensitivity and LABAs prime the glucocorticoid receptor for steroid-dependent activation and enhance cell nuclear translocation. These synergistic interactions are reflected in enhanced anti-inflammatory activity, which has been demonstrated *in vitro* and *in vivo* in a range of inflammatory cells relevant to the pathophysiology of both asthma and COPD. Airway biopsy studies with fluticasone furoate and vilanterol have also shown the synergy between corticosteroids and LABAs to occur at clinical doses of the drugs in patients with COPD.

Clinical efficacy and safety

Asthma

Three phase III randomised, double-blind studies (HZA106827, HZA106829 and HZA106837) of different durations evaluated the safety and efficacy of fluticasone furoate/vilanterol in adult and adolescent patients with persistent asthma. All subjects were using an ICS (Inhaled corticosteroid) with or without LABA for at least 12 weeks prior to visit 1. In HZA106837 all patients had at least one exacerbation that required treatment with oral corticosteroids in the year prior to visit 1. HZA106827 was 12 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 92/22 micrograms [n=201] and FF 92 micrograms [n=205] compared with placebo [n=203], all administered once daily. HZA106829 was 24 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 184/22 micrograms [n=197] and FF 184 micrograms [n=194] both administered once daily compared with FP 500 micrograms twice daily [n=195].

In HZA106827/HZA106829 the co-primary efficacy endpoints were change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at the end of the treatment period in all subjects and weighted mean serial FEV₁ over 0-24 hours post-dose calculated in a subset of subjects at the end of the treatment period. Change from baseline in the percentage of rescue-free 24 hour periods during treatment was a powered secondary endpoint. Results for the primary and key secondary endpoints in these studies are described in Table 1.

Table 1 - Results of primary and key secondary endpoints in HZA106827 and HZA106829

| Study No. | HZA106829 | | HZA106827 | |
|---|--------------------------------------|---|--|---|
| | Treatment Dose of FF/VI*(micrograms) | FF/VI 184/22 Once Daily vs FF 184 Once Daily | FF/VI 184/22 Once Daily vs FP 500 Twice Daily | FF/VI 92/22 Once Daily vs FF 92 Once Daily |
| Change from Baseline in Trough FEV₁ Last Observation Carried Forward (LOCF) | | | | |
| Treatment difference | 193mL | 210mL | 36mL | 172mL |
| P value | p<0.001 | p<0.001 | p=0.405 | p<0.001 |
| (95% CI) | (108, 277) | (127, 294) | (-48, 120) | (87, 258) |
| Weighted Mean Serial FEV₁ over 0-24 hours post-dose | | | | |
| Treatment difference | 136mL | 206mL | 116mL | 302mL |
| P value | p=0.048 | p=0.003 | p=0.06 | p<0.001 |
| (95% CI) | (1, 270) | (73, 339) | (-5, 236) | (178, 426) |
| Change from Baseline in Percentage of Rescue-Free 24-hour Periods | | | | |
| Treatment difference | 11.7% | 6.3% | 10.6% | 19.3% |
| P value | p<0.001 | p=0.067 | p<0.001 | p<0.001 |
| (95% CI) | (4.9, 18.4) | (-0.4, 13.1) | (4.3, 16.8) | (13.0, 25.6) |
| Change from Baseline in Percentage of Symptom-Free 24-hour Periods | | | | |
| Treatment difference | 8.4% | 4.9% | 12.1% | 18.0% |
| P value | p=0.010 | p=0.137 | p<0.001 | p<0.001 |
| (95% CI) | (2.0, 14.8) | (-1.6, 11.3) | (6.2, 18.1) | (12.0, 23.9) |
| Change from Baseline in AM Peak Expiratory Flow | | | | |
| Treatment difference | 33.5L/min | 32.9L/min | 14.6L/min | 33.3L/min |
| P value | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| (95% CI) | (22.3, 41.7) | (24.8, 41.1) | (7.9, 21.3) | (26.5, 40.0) |
| Change from Baseline in PM Peak Expiratory Flow | | | | |
| Treatment difference | 30.7L/min | 26.2L/min | 12.3L/min | 28.2L/min |
| P value | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| (95% CI) | (22.5, 38.9) | (18.0, 34.3) | (5.8, 18.8) | (21.7, 34.8) |

*FF/VI = fluticasone furoate/vilanterol

HZA106837 was of variable treatment duration (from a minimum of 24 weeks to a maximum of 76 weeks with the majority of patients treated for at least 52 weeks). In HZA106837 patients were randomised to receive either fluticasone furoate/vilanterol 92/22 micrograms [n=1009] or FF 92 micrograms [n=1010] both administered once daily. In HZA106837 the primary endpoint was the time to first severe asthma exacerbation. A severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Adjusted mean change from baseline in trough FEV₁ was also evaluated as a secondary endpoint.

In HZA106837 the risk of experiencing a severe asthma exacerbation in patients receiving fluticasone furoate/vilanterol 92/22 micrograms was reduced by 20% compared with FF 92 micrograms alone (hazard ratio 0.795, p=0.036 95% CI 0.642, 0.985). The rate of severe asthma exacerbations per patient per year was 0.19 in the FF 92 micrograms group (approximately 1 in every 5 years) and 0.14 in the fluticasone furoate/vilanterol 92/22 micrograms group (approximately 1 in every 7 years). The ratio of the exacerbation rate for fluticasone furoate/vilanterol 92/22 micrograms versus FF 92 micrograms was 0.755 (95% CI 0.603, 0.945). This represents a 25% reduction in the rate of severe asthma exacerbations for subjects treated with fluticasone furoate/vilanterol 92/22 micrograms compared with FF 92 micrograms (p=0.014). The 24-hour bronchodilator effect of fluticasone furoate/vilanterol was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). Fluticasone furoate/vilanterol 92/22 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV₁ at weeks 12, 36 and 52 and Endpoint compared with FF 92 micrograms (p<0.001 95% CI 52, 126 mL at Endpoint). Forty four percent of patients in the fluticasone furoate/vilanterol 92/22 micrograms group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 92 micrograms group (p<0.001 95% CI 1.23, 1.82).

Studies versus salmeterol/fluticasone propionate combinations

In a 24 week study (HZA113091) in adult and adolescent patients with persistent asthma both fluticasone furoate/vilanterol 92/22 micrograms given once daily in the evening and salmeterol/FP 50/250 micrograms given twice daily demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV₁ of 341 mL (fluticasone furoate/vilanterol) and 377 mL (salmeterol/FP) demonstrated an overall improvement in lung function over 24 hours for both treatments. The adjusted mean treatment difference of 37 mL between the groups was not statistically significant (p=0.162). For trough FEV₁ subjects in the fluticasone furoate/vilanterol group achieved a LS mean change from baseline of 281 mL and subjects in 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.

Fluticasone furoate monotherapy

A 24 week randomised, double-blind placebo controlled study (FFA112059) evaluated the safety and efficacy of FF 92 micrograms once daily [n= 114] and FP 250 micrograms twice daily [n=114] versus placebo [n=115] in adult and adolescent patients with persistent asthma. All subjects had to have been on a stable dose of an ICS for at least 4 weeks prior to visit 1 (screening visit) and the use of LABAs was not permitted within 4 weeks of visit 1. The primary efficacy endpoint was change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at the end of the treatment period. Change from baseline in the percentage of rescue-free 24 hour periods during the 24-week treatment period was a powered secondary. At the 24-week time point FF and FP increased trough FEV₁ by 146 mL (95% CI 36, 257 mL, p=0.009) and 145 mL (95% CI 33, 257 mL, p=0.011) respectively compared to placebo. FF and FP both increased the percentage of 24 hour rescue free periods by 14.8% (95% CI 6.9, 22.7, p<0.001) and 17.9% (95% CI 10.0, 25.7, p<0.001) respectively versus placebo.

Allergen challenge study

The bronchoprotective effect of fluticasone furoate/vilanterol 92/22 micrograms on the early and late asthmatic response to inhaled allergen was evaluated in a repeat dose, placebo-controlled four-way crossover study (HZA113126) in patients with mild asthma. Patients were randomized to receive fluticasone furoate/vilanterol 92/22 micrograms, FF 92 micrograms, vilanterol 22 micrograms or placebo once daily for 21 days followed by challenge with allergen 1 hour after the final dose. The allergen was house dust mite, cat dander, or birch pollen; the selection was based on individual screening tests. Serial FEV₁ measurements were compared with pre-allergen challenge values taken after saline inhalation (baseline). Overall, the greatest effects on the early asthmatic response were seen with fluticasone furoate/vilanterol 92/22 micrograms compared with FF 92 micrograms or vilanterol 22 micrograms alone. Both fluticasone furoate/vilanterol 92/22 micrograms and FF 92 micrograms virtually abolished the late asthmatic response compared with vilanterol alone. Fluticasone furoate/vilanterol 92/22 micrograms provided significantly greater protection against allergen-induced bronchial hyper-reactivity compared with monotherapies FF and vilanterol as assessed on Day 22 by methacholine challenge.

Chronic Obstructive Pulmonary Disease

The COPD clinical development programme included a 12-week (HZA113107), two 6-month (HZA112206, HZA112207) and two one-year (HZA102970, HZA102871) randomised controlled studies in patients with a clinical diagnosis of COPD. These studies included measures of lung function, dyspnoea and moderate and severe exacerbations.

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 fluticasone furoate/vilanterol 46 /22 micrograms [n=206] and fluticasone furoate/vilanterol 92/22 micrograms [n=206] compared with FF 92 micrograms [n=206], vilanterol 22 micrograms [n=205] and placebo [n = 207], all administered once daily. HZC112207 evaluated the efficacy of fluticasone furoate/vilanterol 92/22 micrograms [n=204] and fluticasone furoate/vilanterol 184/22 micrograms [n=205] compared with FF 92 micrograms [n=204], FF 184 micrograms [n=203] and vilanterol 22 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 FEV₁/FVC ratio less than or equal to 0.70; post-salbutamol FEV₁ less than or equal to 70% predicted and have a Modified Medical Research Council (mMRC) dyspnea score ≥ 2 (scale 0-4) at screening. At screening, the mean pre-bronchodilator FEV₁ was 42.6% and 43.6% predicted, and the mean reversibility was 15.9% and 12.0% in HZC112206 and HZC112207, respectively. The co-primary endpoints in both studies were weighted mean FEV₁ from zero to 4 hours post-dose at Day 168 and change from baseline in pre-dose trough FEV₁ at Day 169.

In an integrated analysis of both studies, fluticasone furoate/vilanterol 92/22 micrograms showed clinically meaningful improvements in lung function. At Day 169 fluticasone furoate/vilanterol 92/22 micrograms and vilanterol increased adjusted mean trough FEV₁ by 129 mL (95% CI: 91, 167 mL, p<0.001) and 83 mL (95% CI: 46, 121mL, p<0.001) respectively compared to placebo. Fluticasone furoate/vilanterol 92/22 micrograms increased trough FEV₁ by 46 mL compared to vilanterol (95% CI: 8, 83mL, p= 0.017). At Day 168 fluticasone furoate/vilanterol 92/22 micrograms and vilanterol increased adjusted mean weighted mean FEV₁ over 0-4 hours by 193mL (95% CI: 156, 230 mL, p<0.001) and 145 mL (95% CI: 108, 181 mL, p<0.001) respectively compared to placebo. Fluticasone furoate/vilanterol 92/22 micrograms increased adjusted mean weighted mean FEV₁ over 0-4 hours by 148 ml compared to FF alone (95% CI: 112, 184 mL, p< 0.001).

12 month studies

Studies HZC102970 and HZC102871 were 52 week randomised, double-blind, parallel-group, studies comparing the effect of fluticasone furoate/vilanterol 184/22 micrograms, fluticasone furoate/vilanterol 92/22 micrograms, fluticasone furoate/vilanterol 46/22 micrograms with vilanterol 22 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 FEV₁/FVC ratio less than or equal to 0.70 and post-salbutamol FEV₁ 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. 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 period 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 (beta₂-agonist and anticholinergic), ipratropium/salbutamol combination products, oral beta₂-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 fluticasone furoate/vilanterol 92/22 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) | fluticasone furoate/vilanterol 92/22 (n=403) | Vilanterol (n=409) | fluticasone furoate/vilanterol 92/22 (n=403) | Vilanterol (n=818) | fluticasone furoate/vilanterol 92/22 (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 | | 0.79 | | 0.66 | | 0.73 |
| 95% CI | | (0.64,0.97) | | (0.54, 0.81) | | (0.63, 0.84) |
| p-value | | 0.024 | | <0.001 | | <0.001 |
| % reduction | | 21 | | 34 | | 27 |
| (95% CI) | | (3, 36) | | (19, 46) | | (16, 37) |
| Absolute difference in number per year vs VI (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) | | 0.80 (0.66, 0.99) | | 0.72 (0.59, 0.89) | | 0.76 (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 fluticasone furoate/vilanterol 92/22 micrograms versus vilanterol 22 micrograms in adjusted mean trough FEV₁ (42 mL 95% CI: 19, 64mL, p<0.001). The 24-hour bronchodilator effect of fluticasone furoate/vilanterol was maintained from the first dose throughout 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, fluticasone furoate/vilanterol 92/22 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 fluticasone furoate/vilanterol 92/22 micrograms vs. vilanterol 22 micrograms in adjusted mean trough FEV₁ (44 mL 95% CI: 15, 73mL, (p=0.003)).

Studies versus salmeterol/fluticasone propionate combinations

In a 12 week study (HZC113107) in COPD patients both fluticasone furoate/vilanterol 92/22 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 FEV₁ 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, 63mL) between the groups was not statistically significant (p=0.282). The adjusted mean change from baseline in trough FEV₁ 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/FP or versus other established bronchodilators have been conducted to appropriately compare the effects on COPD exacerbations.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Relvar Ellipta in all subsets of the paediatric population in COPD (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Relvar Ellipta in one or more subsets of the paediatric population in asthma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability for fluticasone furoate and vilanterol when administered by inhalation as fluticasone furoate/vilanterol was on average 15.2% and 27.3%, respectively. The oral bioavailability of both fluticasone furoate and vilanterol was low, on average 1.26% and <2%, respectively. Given this low oral bioavailability, systemic exposure for fluticasone furoate and vilanterol following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Distribution

Following intravenous dosing, both fluticasone furoate and vilanterol are extensively distributed with average volumes of distribution at steady state of 661 L and 165 L, respectively.

Both fluticasone furoate and vilanterol have a low association with red blood cells. In vitro plasma protein binding in human plasma of fluticasone furoate and vilanterol was high, on average >99.6% and 93.9%, respectively. There was no decrease in the extent of in vitro plasma protein binding in subjects with renal or hepatic impairment.

Fluticasone furoate and vilanterol are substrates for P-glycoprotein (P-gp), however, concomitant administration of fluticasone furoate/vilanterol with P-gp inhibitors is considered unlikely to alter fluticasone furoate or vilanterol systemic exposure since they are both well absorbed molecules.

Biotransformation

Based on *in vitro* data, the major routes of metabolism of both fluticasone furoate and vilanterol in human are mediated primarily by CYP3A4.

Fluticasone furoate is primarily metabolised through hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity. Vilanterol is primarily metabolised by O-dealkylation to a range of metabolites with significantly reduced β_1 - and β_2 -agonist activity.

Elimination

Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine.

Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively in a human radiolabel study conducted by the oral route. The apparent plasma elimination half-life of vilanterol following single inhaled administration of fluticasone furoate/vilanterol was, on average, 2.5 hours. The

effective half-life for accumulation of vilanterol, as determined from inhalation administration of repeat doses of vilanterol 25 micrograms, is 16.0 hours in subjects with asthma and 21.3 hours in subjects with COPD.

Paediatric population

In adolescents (12 years or older), there are no recommended dose modifications.

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

Special populations

Elderly patients (> 65 years old)

The effects of age on the pharmacokinetics of fluticasone furoate and vilanterol were determined in phase III studies in COPD and asthma. There was no evidence for age (12-84) to affect the pharmacokinetics of fluticasone furoate and vilanterol in subjects with asthma.

There was no evidence for age to affect the pharmacokinetics of fluticasone furoate in subjects with COPD while there was an increase (37%) in AUC₍₀₋₂₄₎ of vilanterol over the observed age range of 41 to 84 years. For an elderly subject (aged 84 years) with low bodyweight (35 kg) vilanterol AUC₍₀₋₂₄₎ is predicted to be 35% higher than the population estimate (subject with COPD aged 60 years and bodyweight of 70 kg), whilst C_{max} was unchanged. These differences are unlikely to be of clinical relevance. In subjects with asthma and subjects with COPD there are no recommended dose modifications.

Renal impairment

A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or beta₂-agonist systemic effects compared with healthy subjects.

No dose adjustment is required for patients with renal impairment.

The effects of haemodialysis have not been studied.

Hepatic impairment

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by AUC₍₀₋₂₄₎) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (Child-Pugh B; fluticasone furoate/vilanterol 184/22 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. Dose-normalised fluticasone furoate systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B or C).

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, 22 micrograms) or with severe hepatic impairment (vilanterol, 12.5 micrograms) compared with healthy subjects.

Other special populations

In subjects with asthma, estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects (12-13% of subjects) were on average 33% to 53% higher compared with other racial groups. However, there was no evidence for the higher systemic exposure in this population to be associated with greater effect on 24 hour urinary cortisol excretion. On average, vilanterol C_{max} is predicted to be 220 to 287% higher and $AUC_{(0-24)}$ comparable for those subjects from an Asian heritage compared with subjects from other racial groups. However, there was no evidence that this higher vilanterol C_{max} resulted in clinically significant effects on heart rate.

In subjects with COPD estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects (13-14% subjects) were on average 23% to 30% higher compared with Caucasian subjects. However, there was no evidence for the higher systemic exposure in this population to be associated with greater effect on 24 hour urinary cortisol excretion. There was no effect of race on pharmacokinetic parameter estimates of vilanterol in subjects with COPD.

Gender, weight and BMI

There was no evidence for gender, weight or BMI (body mass index) to influence the pharmacokinetics of fluticasone furoate based on a population pharmacokinetic analysis of phase III data in 1213 subjects with asthma (712 females) 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 BMI.

5.3 Preclinical safety data

Pharmacological and toxicological effects seen with fluticasone furoate or vilanterol in nonclinical studies were those typically associated with either glucocorticoids or beta₂-agonists. Administration of fluticasone furoate combined with vilanterol did not result in any significant new toxicity.

Genotoxicity and carcinogenicity

Fluticasone furoate

Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures similar to those at the maximum recommended human dose, based on AUC.

Vilanterol trifenate

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

Consistent with findings for other beta₂ agonists, in lifetime inhalation studies vilanterol trifenate caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Reproductive toxicity

Fluticasone furoate

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

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

Vilanterol trifenate

Vilanterol trifenate was not teratogenic in rats. In inhalation studies in rabbits, vilanterol trifenate caused effects similar to those seen with other beta₂ agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 84-times greater than those at the maximum recommended human dose, based on AUC.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

In-use shelf-life after opening the tray: 6 weeks.

6.4 Special precautions for storage

Do not store above 25°C. If stored in a refrigerator allow the inhaler to return to room temperature for at least an hour before use.

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

To be used within 6 weeks of first opening of the tray.

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

6.5 Nature and contents of container

The inhaler consists of a light grey body, a yellow 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 aluminium foil laminate strips of 14 or 30 doses.

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

Pack sizes of 14 or 30 dose Inhalers. Multipack of 3 x 30 dose Inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

For instructions for use, see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/886/001
EU/1/13/886/002
EU/1/13/886/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Each delivered dose contains approximately 25 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation powder, pre-dispensed
(Inhalation powder).

White powder in a light grey inhaler with a yellow mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Asthma

Relvar Ellipta is indicated for the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination medicinal product (long-acting beta₂-agonist and inhaled corticosteroid) is appropriate:

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

4.2 Posology and method of administration

Posology

Asthma

Adults and adolescents aged 12 years and over

One inhalation of Relvar Ellipta 184/22 micrograms once daily.

Patients usually experience an improvement in lung function within 15 minutes of inhaling Relvar Ellipta. However, the patient should be informed that regular daily usage is necessary to maintain control of asthma symptoms and that use should be continued even when asymptomatic.

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

A starting dose of Relvar Ellipta 92/22 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid dose of inhaled corticosteroid in combination with a long-acting beta₂-agonist. If patients are inadequately controlled on Relvar Ellipta 92/22 micrograms, the dose can be increased to 184/22 micrograms, which may provide additional improvement in asthma control.

Patients should be regularly reassessed by a healthcare professional so that the strength of fluticasone furoate/vilanterol they are receiving remains optimal and is only changed on medical advice. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Relvar Ellipta 184/22 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of inhaled corticosteroid in combination with a long-acting beta₂-agonist.

The maximum recommended dose is Relvar Ellipta 184/22 micrograms once daily.

Patients with asthma should be given the strength of Relvar Ellipta containing the appropriate fluticasone furoate (FF) dosage for the severity of their disease. Prescribers should be aware that in patients with asthma, fluticasone furoate (FF) 100 micrograms once daily is approximately equivalent to fluticasone propionate (FP) 250 micrograms twice daily, while FF 200 micrograms once daily is approximately equivalent to FP 500 micrograms twice daily.

Children aged under 12 years

The safety and efficacy of Relvar Ellipta in children under 12 years of age has not yet been established in the indication for asthma.

No data are available.

Special populations

Elderly patients (>65 years)

No dose adjustment is required in this population (see section 5.2).

Renal impairment

No dose adjustment is required in this population (see section 5.2).

Hepatic impairment

Studies in subjects with mild, moderate and severe hepatic impairment showed an increase in systemic exposure to fluticasone furoate (both C_{max} and AUC) (see section 5.2).

Caution should be exercised when dosing patients with hepatic impairment who may be more at risk of systemic adverse reactions associated with corticosteroids.

For patients with moderate or severe hepatic impairment the maximum dose is 92/22 micrograms (see section 4.4).

Method of administration

Relvar Ellipta is for inhalation use only.

It should be administered at the same time of the day, each day.

The final decision on evening or morning dosing should be left to the discretion of the physician.

If a dose is missed the next dose should be taken at the usual time the next day.

If stored in a refrigerator, the inhaler should be allowed to return to room temperature for at least an hour before use.

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

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

The Ellipta inhaler is packaged in a tray containing a desiccant sachet, to reduce moisture. Once opened the desiccant sachet should be discarded.

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

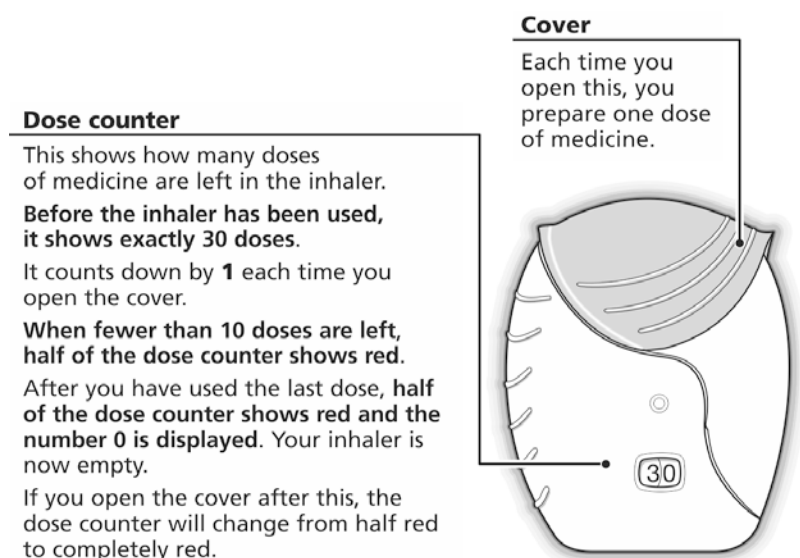
When the inhaler is taken out of its tray, it will be in the 'closed' position. The "Discard by" date should be written on the inhaler label in the space provided. The "Discard by" date is 6 weeks from the date of opening the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

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

Instructions for use

1. Read this before you start

If the inhaler cover is opened and closed without inhaling the medicine, the dose will be lost. The lost dose will be securely held inside the inhaler, but it will no longer be available to be inhaled. It is not possible to accidentally take extra medicine or a double dose in one inhalation.



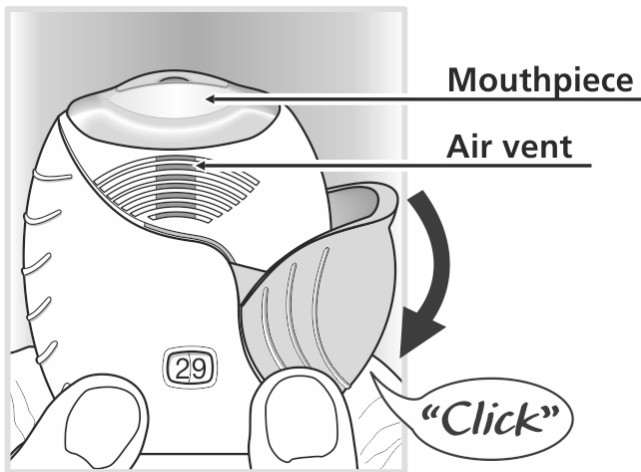
2. How to prepare a dose

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

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

The medicine is now ready to be inhaled. The dose counter counts down by 1 to confirm.

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



3. How to inhale the medicine

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

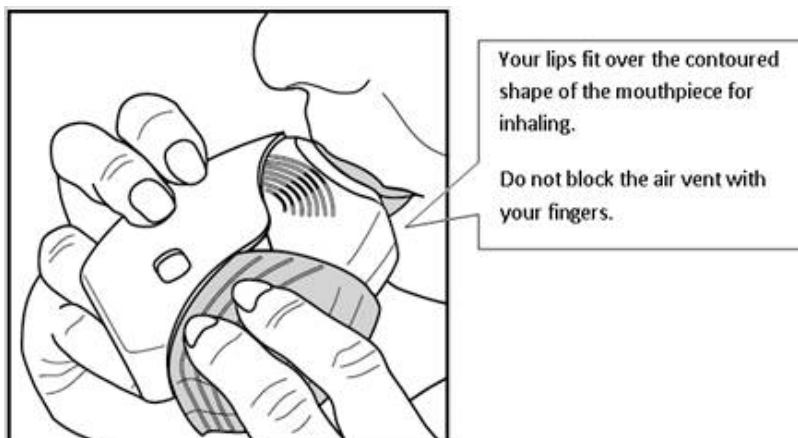
Do not breathe out into the inhaler.

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

Do not block the air-vents with your fingers.

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

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



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

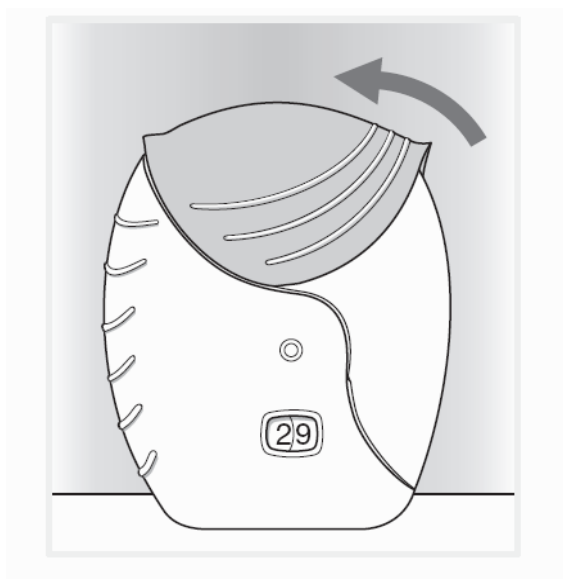
4. Close the inhaler and rinse your mouth

If you want to clean the mouthpiece, use a **dry tissue**, **before** closing 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 to develop a sore mouth or throat as side effects.



4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Deterioration of disease

Fluticasone furoate/vilanterol should not be used to treat acute asthma symptoms, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop therapy with fluticasone furoate/vilanterol in asthma, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with fluticasone furoate/vilanterol. Patients should be asked to continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with Relvar Ellipta.

Paradoxical bronchospasm

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. Relvar Ellipta should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including Relvar Ellipta. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease or heart rhythm abnormalities, thyrotoxicosis, uncorrected hypokalaemia or patients predisposed to low levels of serum potassium.

Patients with hepatic impairment

For patients with moderate to severe hepatic impairment, the 92/22 micrograms dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions (see section 5.2).

Systemic corticosteroid effects

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Fluticasone furoate/vilanterol should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Hyperglycaemia

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

Pneumonia in patients with COPD

An increase in the incidence of pneumonia, including pneumonia requiring hospitalisation, has been observed in patients with COPD receiving inhaled corticosteroids. There is some evidence of an increased risk of pneumonia with increasing steroid dose but this has not been demonstrated conclusively across all studies.

There is no conclusive clinical evidence for intra-class differences in the magnitude of the pneumonia risk among inhaled corticosteroid products.

Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations.

Risk factors for pneumonia in patients with COPD include current smoking, older age, low body mass index (BMI) and severe COPD.

Relvar Ellipta 184/22 micrograms is not indicated for patients with COPD. There is no additional benefit of the 184/22 micrograms dose compared to the 92/22 micrograms dose and there is a potential increased risk of systemic corticosteroid-related adverse reactions (see section 4.8).

Pneumonia in patients with asthma

The incidence of pneumonia in patients with asthma was common at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 184/22 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 92/22 micrograms or placebo (see section 4.8). No risk factors were identified.

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Clinically significant drug interactions mediated by fluticasone furoate/vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

Beta₂-adrenergic blockers may weaken or antagonise the effect of beta₂-adrenergic agonists. Concurrent use of both non-selective and selective beta₂-adrenergic blockers should be avoided unless there are compelling reasons for their use.

Interaction with CYP3A4 inhibitors

Fluticasone furoate and vilanterol are both rapidly cleared by extensive first pass metabolism mediated by the liver enzyme CYP3A4.

Caution is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for increased systemic exposure to both fluticasone furoate and vilanterol, and concomitant use should be avoided. A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (184/22 micrograms) and the strong CYP3A4 inhibitor ketoconazole (400mg). Co-administration increased mean fluticasone furoate AUC₍₀₋₂₄₎ and C_{max} by 36% and 33%, respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 hours weighted mean serum cortisol. Co-administration increased mean vilanterol AUC_(0-t) and C_{max} 65% and 22%, respectively. The increase in vilanterol exposure was not associated with an increase in beta₂-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Interaction with P-glycoprotein inhibitors

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

Sympathomimetic medicinal products

Concomitant administration of other sympathomimetic medicinal products (alone or as part of combination therapy) may potentiate the adverse reactions of fluticasone furoate/vilanterol. Relvar Ellipta should not be used in conjunction with other long-acting beta₂-adrenergic agonists or medicinal products containing long-acting beta₂-adrenergic agonists.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant (see section 5.3). There are no or limited data from the use of fluticasone furoate and vilanterol trifenate in pregnant women.

Administration of fluticasone furoate/vilanterol to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Breast-feeding

There is insufficient information on the excretion of fluticasone furoate or vilanterol trifenate and/or metabolites in human milk. However, other corticosteroids and beta₂-agonists are detected in human milk (see section 5.3). A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue fluticasone furoate/vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no effect of fluticasone furoate/vilanterol trifenate on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Fluticasone furoate or vilanterol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with fluticasone furoate/vilanterol. In the asthma clinical development program a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development programme a total of 6,237 subjects were included in an integrated assessment of adverse reactions.

The most commonly reported adverse reactions with fluticasone furoate and vilanterol were headache and nasopharyngitis. With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently commonly observed in patients with COPD.

Tabulated list of adverse reactions

Adverse reactions are listed by system organ class and frequency. The following convention has been used for the classification of frequencies: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| System organ class | Adverse reaction(s) | Frequency |
|--|---|--------------------------|
| Infections and infestations | Pneumonia* Upper respiratory tract infection Bronchitis Influenza Candidiasis of mouth and throat | Common |
| Immune system disorders | Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria. | Rare |
| Nervous system disorders | Headache Tremor | Very common Rare |
| Psychiatric disorders | Anxiety | Rare |
| Cardiac disorders | Extrasystoles Palpitations Tachycardia | Uncommon Rare Rare |
| Respiratory, thoracic and mediastinal disorders | Nasopharyngitis Oropharyngeal pain Sinusitis Pharyngitis Rhinitis Cough Dysphonia | Very common Common |
| Gastrointestinal disorders | Abdominal pain | Common |
| Musculoskeletal and connective tissue disorders | Arthralgia Back pain Fractures** Muscle spasms | Common |
| General disorders and administration site conditions | Pyrexia | Common |

*, ** See below 'Description of selected adverse reactions'

Description of selected adverse reactions

Pneumonia

In an integrated analysis of the two replicate one year studies in COPD with an exacerbation in the preceding year (n = 3255), the number of pneumonia events per 1000 patient years was 97.9 with FF/VI 184/22, 85.7 in the FF/VI 92/22 and 42.3 in the VI 22 group. For severe pneumonia the corresponding number of events per 1000 patient years were 33.6, 35.5, and 7.6 respectively, while for serious pneumonia the corresponding events per 1000 patient years were 35.1 for FF/VI 184/22, 42.9 with FF/VI 92/22, 12.1 with VI 22. Finally, the exposure-adjusted cases of fatal pneumonia were 8.8 for FF/VI 184/22 versus 1.5 for FF/VI 92/22 and 0 for VI 22.

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia per 1000 patient years was 18.4 for FF/VI 184/22 versus 9.6 for FF/VI 92/22 and 8.0 in the placebo group.

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 22 micrograms group (<1%). Although there were more fractures in the Relvar Ellipta groups compared with the vilanterol 22 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Symptoms and signs

An overdose of fluticasone furoate/vilanterol may produce signs and symptoms due to the individual component's actions, including those seen with overdose of other beta₂-agonists and consistent with the known inhaled corticosteroid class effects (see section 4.4).

Treatment

There is no specific treatment for an overdose with fluticasone furoate/vilanterol. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

Cardioselective beta-blockade should only be considered for profound vilanterol overdose effects that are clinically concerning and unresponsive to supportive measures. Cardioselective beta-blocking medicinal products should be used with caution in patients with a history of bronchospasm.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airways diseases, Adrenergics and other drugs for obstructive airway diseases, ATC code: R03AK10.

Mechanism of action

Fluticasone furoate and vilanterol represent two classes of medications (a synthetic corticosteroid and a selective, long-acting beta₂-receptor agonist).

Pharmacodynamic effects

Fluticasone furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. The precise mechanism through which fluticasone furoate affects asthma and COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g. eosinophils, macrophages, lymphocytes) and mediators (e.g. cytokines and chemokines involved in inflammation).

Vilanterol trifenate

Vilanterol trifenate is a selective long-acting, beta₂-adrenergic agonist (LABA). The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including vilanterol trifenate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the beta₂-receptor gene, increasing receptor number and sensitivity and LABAs prime the glucocorticoid receptor for steroid-dependent activation and enhance cell nuclear translocation. These synergistic interactions are reflected in enhanced anti-inflammatory activity, which has been demonstrated *in vitro* and *in vivo* in a range of inflammatory cells relevant to the pathophysiology of both asthma and COPD. Airway biopsy studies with fluticasone furoate and vilanterol have also shown the synergy between corticosteroids and LABAs to occur at clinical doses of the drugs in patients with COPD.

Clinical efficacy and safety

Asthma

Three phase III randomised, double-blind studies (HZA106827, HZA106829 and HZA106837) of different durations evaluated the safety and efficacy of fluticasone furoate/vilanterol in adult and adolescent patients with persistent asthma. All subjects were using an ICS (Inhaled corticosteroid) with or without LABA for at least 12 weeks prior to visit 1. In HZA106837 all patients had at least one exacerbation that required treatment with oral corticosteroids in the year prior to visit 1. HZA106827 was 12 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 92/22 micrograms [n=201] and FF 92 micrograms [n=205]) compared with placebo [n=203], all administered once daily. HZA106829 was 24 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 184/22 micrograms [n=197] and FF 184 micrograms [n=194]) both administered once daily compared with FP 500 micrograms twice daily [n=195].

In HZA106827/HZA106829 the co-primary efficacy endpoints were change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at the end of the treatment period in all subjects and weighted mean serial FEV₁ over 0-24 hours post-dose calculated in a subset of subjects at the end of the treatment period. Change from baseline in the percentage of rescue-free 24 hour periods during treatment was a powered secondary endpoint. Results for the primary and key secondary endpoints in these studies are described in Table 1.

Table 1 - Results of primary and key secondary endpoints in HZA106827 and HZA106829

| Study No. | HZA106829 | | HZA106827 | |
|---|---|--|---|---|
| Treatment Dose of FF/VI*(micrograms) | FF/VI 184/22 Once Daily vs FF 184 Once Daily | FF/VI 184/22 Once Daily vs FP 500 Twice Daily | FF/VI 92/22 Once Daily vs FF 92 Once Daily | FF/VI 92/22 Once Daily vs placebo Once Daily |
| Change from Baseline in Trough FEV₁ Last Observation Carried Forward (LOCF) | | | | |
| Treatment difference | 193mL | 210mL | 36mL | 172mL |
| P value | p<0.001 | p<0.001 | p=0.405 | p<0.001 |
| (95% CI) | (108, 277) | (127, 294) | (-48, 120) | (87, 258) |

| Study No. | HZA106829 | | HZA106827 | |
|---|--------------|--------------|-------------|--------------|
| Weighted Mean Serial FEV₁ over 0-24 hours post-dose | | | | |
| Treatment difference | 136mL | 206mL | 116mL | 302mL |
| P value | p=0.048 | p=0.003 | p=0.06 | p<0.001 |
| (95% CI) | (1, 270) | (73, 339) | (-5, 236) | (178, 426) |
| Change from Baseline in Percentage of Rescue-Free 24-hour Periods | | | | |
| Treatment difference | 11.7% | 6.3% | 10.6% | 19.3% |
| P value | p<0.001 | p=0.067 | p<0.001 | p<0.001 |
| (95% CI) | (4.9, 18.4) | (-0.4, 13.1) | (4.3, 16.8) | (13.0, 25.6) |
| Change from Baseline in Percentage of Symptom-Free 24-hour Periods | | | | |
| Treatment difference | 8.4% | 4.9% | 12.1% | 18.0% |
| P value | p=0.010 | p=0.137 | p<0.001 | p<0.001 |
| (95% CI) | (2.0, 14.8) | (-1.6, 11.3) | (6.2, 18.1) | (12.0, 23.9) |
| Change from Baseline in AM Peak Expiratory Flow | | | | |
| Treatment difference | 33.5L/min | 32.9L/min | 14.6L/min | 33.3L/min |
| P value | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| (95% CI) | (22.3, 41.7) | (24.8, 41.1) | (7.9, 21.3) | (26.5, 40.0) |
| Change from Baseline in PM Peak Expiratory Flow | | | | |
| Treatment difference | 30.7L/min | 26.2L/min | 12.3L/min | 28.2L/min |
| P value | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| (95% CI) | (22.5, 38.9) | (18.0, 34.3) | (5.8, 18.8) | (21.7, 34.8) |

*FF/VI = fluticasone furoate/vilanterol

HZA106837 was of variable treatment duration (from a minimum of 24 weeks to a maximum of 76 weeks with the majority of patients treated for at least 52 weeks). In HZA106837 patients were randomised to receive either fluticasone furoate/vilanterol 92/22 micrograms [n=1009] or FF 92 micrograms [n=1010] both administered once daily. In HZA106837 the primary endpoint was the time to first severe asthma exacerbation. A severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Adjusted mean change from baseline in trough FEV₁ was also evaluated as a secondary endpoint.

In HZA106837 the risk of experiencing a severe asthma exacerbation in patients receiving fluticasone furoate/vilanterol 92/22 micrograms was reduced by 20% compared with FF 92 micrograms alone (hazard ratio 0.795, p=0.036 95% CI 0.642, 0.985). The rate of severe asthma exacerbations per patient per year was 0.19 in the FF 92 group (approximately 1 in every 5 years) and 0.14 in the fluticasone furoate/vilanterol 92/22 micrograms group (approximately 1 in every 7 years). The ratio of the exacerbation rate for fluticasone furoate/vilanterol 92/22 micrograms versus FF 92 was 0.755 (95% CI 0.603, 0.945). This represents a 25% reduction in the rate of severe asthma exacerbations for subjects treated with fluticasone furoate/vilanterol 92/22 micrograms compared with FF 92 (p=0.014). The 24-hour bronchodilator effect of fluticasone furoate/vilanterol was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). Fluticasone furoate/vilanterol 92 /22 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV₁ at weeks 12, 36 and 52 and Endpoint compared with FF 92 micrograms (p<0.001 95% CI 52, 126 mL at Endpoint). Forty four percent of patients in the fluticasone furoate/vilanterol 92/22 group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 92 micrograms group (p<0.001 95% CI 1.23, 1.82).

Studies versus salmeterol/fluticasone propionate combinations

In a 24 week study (HZA113091) in adult and adolescent patients with persistent asthma both fluticasone furoate/vilanterol 92/22 micrograms given once daily in the evening and salmeterol/FP 50/250 micrograms given twice daily demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV₁ of 341 mL (fluticasone furoate/vilanterol) and 377 mL (salmeterol/FP) demonstrated an overall improvement in lung function over 24 hours for both treatments. The adjusted mean treatment difference of 37 mL between the groups was not statistically

significant ($p=0.162$). For trough FEV₁ subjects in the fluticasone furoate/vilanterol group achieved a LS mean change from baseline of 281 mL and subjects in salmeterol/FP group a change of 300 mL; (the difference in adjusted mean of 19 mL (95% CI:-0.073, 0.034) was not statistically significant ($p=0.485$).

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

Fluticasone furoate monotherapy

A 24 week randomised, double-blind placebo controlled study (FFA112059) evaluated the safety and efficacy of FF 92 micrograms once daily [$n=114$] and FP 250 micrograms twice daily [$n=114$] versus placebo [$n=115$] in adult and adolescent patients with persistent asthma. All subjects had to have been on a stable dose of an ICS for at least 4 weeks prior to visit 1 (screening visit) and the use of LABAs was not permitted within 4 weeks of visit 1. The primary efficacy endpoint was change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV₁ at the end of the treatment period. Change from baseline in the percentage of rescue-free 24 hour periods during the 24-week treatment period was a powered secondary. At the 24-week time point FF and FP increased trough FEV₁ by 146 mL (95% CI 36, 257 mL, $p=0.009$) and 145 mL (95% CI 33, 257 mL, $p=0.011$) respectively compared to placebo. FF and FP both increased the percentage of 24 hour rescue free periods by 14.8% (95% CI 6.9, 22.7, $p<0.001$) and 17.9% (95% CI 10.0, 25.7, $p<0.001$) respectively versus placebo.

Allergen challenge study

The bronchoprotective effect of fluticasone furoate/vilanterol 92/22 micrograms on the early and late asthmatic response to inhaled allergen was evaluated in a repeat dose, placebo-controlled four-way crossover study (HZA113126) in patients with mild asthma. Patients were randomized to receive fluticasone furoate/vilanterol 92/22 micrograms, FF 92 micrograms, vilanterol 22 micrograms or placebo once daily for 21 days followed by challenge with allergen 1 hour after the final dose. The allergen was house dust mite, cat dander, or birch pollen; the selection was based on individual screening tests. Serial FEV₁ measurements were compared with pre-allergen challenge values taken after saline inhalation (baseline). Overall, the greatest effects on the early asthmatic response were seen with fluticasone furoate/vilanterol 92/22 micrograms compared with FF 92 micrograms or vilanterol 22 micrograms alone. Both fluticasone furoate/vilanterol 92/22 micrograms and FF 92 micrograms virtually abolished the late asthmatic response compared with vilanterol alone. Fluticasone furoate/vilanterol 92/22 micrograms provided significantly greater protection against allergen-induced bronchial hyper-reactivity compared with monotherapies FF and vilanterol as assessed on Day 22 by methacholine challenge.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Relvar Ellipta in one or more subsets of the paediatric population in asthma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability for fluticasone furoate and vilanterol when administered by inhalation as fluticasone furoate/vilanterol was on average 15.2% and 27.3%, respectively. The oral bioavailability of both fluticasone furoate and vilanterol was low, on average 1.26% and <2%, respectively. Given this low oral bioavailability, systemic exposure for fluticasone furoate and vilanterol following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Distribution

Following intravenous dosing, both fluticasone furoate and vilanterol are extensively distributed with average volumes of distribution at steady state of 661 L and 165 L, respectively.

Both fluticasone furoate and vilanterol have a low association with red blood cells. In vitro plasma protein binding in human plasma of fluticasone furoate and vilanterol was high, on average >99.6% and 93.9%, respectively. There was no decrease in the extent of in vitro plasma protein binding in subjects with renal or hepatic impairment.

Fluticasone furoate and vilanterol are substrates for P-glycoprotein (P-gp), however, concomitant administration of fluticasone furoate/vilanterol with P-gp inhibitors is considered unlikely to alter fluticasone furoate or vilanterol systemic exposure since they are both well absorbed molecules.

Biotransformation

Based on *in vitro* data, the major routes of metabolism of both fluticasone furoate and vilanterol in human are mediated primarily by CYP3A4.

Fluticasone furoate is primarily metabolised through hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity. Vilanterol is primarily metabolised by O-dealkylation to a range of metabolites with significantly reduced β_1 - and β_2 -agonist activity.

Elimination

Following oral administration, fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine.

Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively in a human radiolabel study conducted by the oral route. The apparent plasma elimination half-life of vilanterol following single inhaled administration of fluticasone furoate/vilanterol was, on average, 2.5 hours. The effective half-life for accumulation of vilanterol, as determined from inhalation administration of repeat doses of vilanterol 25 micrograms, is 16.0 hours in subjects with asthma and 21.3 hours in subjects with COPD.

Paediatric population

In adolescents (12 years or older), there are no recommended dose modifications.

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

Special populations

Elderly patients (> 65 years old)

The effects of age on the pharmacokinetics of fluticasone furoate and vilanterol were determined in phase III studies in COPD and asthma. There was no evidence for age (12-84) to affect the pharmacokinetics of fluticasone furoate and vilanterol in subjects with asthma.

In subjects with asthma and subjects with COPD there are no recommended dose modifications.

Renal impairment

A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or beta₂-agonist systemic effects compared with healthy subjects.

No dose adjustment is required for patients with renal impairment.

The effects of haemodialysis have not been studied.

Hepatic impairment

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0-24)}$) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure in subjects with moderate hepatic impairment (Child-Pugh B; fluticasone furoate/vilanterol 184/22 micrograms) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. Dose-normalised fluticasone furoate systemic exposure was similar in subjects with moderate and severe hepatic impairment (Child-Pugh B or C).

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, 22 micrograms) or with severe hepatic impairment (vilanterol, 12.5 micrograms) compared with healthy subjects.

Other special populations

In subjects with asthma, estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South East Asian subjects (12-13% of subjects) were on average 33% to 53% higher compared with other racial groups. However, there was no evidence for the higher systemic exposure in this population to be associated with greater effect on 24 hour urinary cortisol excretion. On average, vilanterol C_{max} is predicted to be 220 to 287% higher and $AUC_{(0-24)}$ comparable for those subjects from an Asian heritage compared with subjects from other racial groups. However, there was no evidence that this higher vilanterol C_{max} resulted in clinically significant effects on heart rate.

Gender, weight and BMI

There was no evidence for gender, weight or BMI (body mass index) to influence the pharmacokinetics of fluticasone furoate based on a population pharmacokinetic analysis of phase III data in 1213 subjects with asthma (712 females).

There was no evidence for gender, weight or BMI to influence the pharmacokinetics of vilanterol based on a population pharmacokinetic analysis in 856 subjects with asthma (500 females).

No dosage adjustment is necessary based on gender, weight or BMI.

5.3 Preclinical safety data

Pharmacological and toxicological effects seen with fluticasone furoate or vilanterol in nonclinical studies were those typically associated with either glucocorticoids or beta₂-agonists. Administration of fluticasone furoate combined with vilanterol did not result in any significant new toxicity.

Genotoxicity and carcinogenicity

Fluticasone furoate

Fluticasone furoate was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures similar to those at the maximum recommended human dose, based on AUC.

Vilanterol trifenate

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

Consistent with findings for other beta₂ agonists, in lifetime inhalation studies vilanterol trifenate caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Reproductive toxicity

Fluticasone furoate

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

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

Vilanterol trifenate

Vilanterol trifenate was not teratogenic in rats. In inhalation studies in rabbits, vilanterol trifenate caused effects similar to those seen with other beta₂ agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation). When given subcutaneously there were no effects at exposures 84-times greater than those at the maximum recommended human dose, based on AUC.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
In-use shelf-life after opening the tray: 6 weeks.

6.4 Special precautions for storage

Do not store above 25°C. If stored in a refrigerator allow the inhaler to return to room temperature for at least an hour before use.

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

To be used within 6 weeks of first opening of the tray

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

6.5 Nature and contents of container

The inhaler consists of a light grey body, a yellow 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 aluminium foil laminate strips of 14 or 30 doses.

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

Pack sizes of 14 or 30 dose Inhalers. Multipack of 3 x 30 dose Inhalers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

For instructions for use, see section 4.2.

7. MARKETING AUTHORISATION HOLDER

Glaxo Group Limited
980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/886/004
EU/1/13/886/005
EU/1/13/886/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 November 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Glaxo Operations UK Ltd. (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Hertfordshire SG12 0DJ
United Kingdom

Glaxo Operations UK Ltd. (trading as Glaxo Wellcome Operations),
Harmire Road,
Barnard Castle,
County Durham DL12 8DT,
United Kingdom.

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal products subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk Management Plan (RMP)

The MAH shall perform the required Pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (Pharmacovigilance or risk minimisation) milestone being reached.
- <Obligation to conduct post-authorisation measures>

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|--|-------------|
| Submission of final clinical study report for the interventional post-authorisation safety | 31 December |

| | |
|---|--------------|
| study to further investigate the risk of pneumonia with Relvar Ellipta compared with other ICS/LABA FDC in the treatment of COPD, according to a protocol agreed by the Committee. | 2016 |
| Submission of final clinical study report for the interventional post-authorisation safety study to further investigate the risk of pneumonia with Relvar Ellipta compared with other ICS/LABA FDC in the treatment of asthma, according to a protocol agreed by the Committee. | 30 June 2018 |

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (SINGLE PACKS & MULTIPACK ONLY)

92/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed

fluticasone furoate/vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate).

3. LIST OF EXCIPIENTS

Also contains lactose and magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed.

14 doses

30 doses

3 x 30 doses

1 inhaler of 14 doses

1 inhaler of 30 doses

Multipack: 90 (3 packs of 30) doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use,
ONCE DAILY

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

In use shelf-life: 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/886/001

EU/1/13/886/002

EU/1/13/886/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

relvar ellipta 92:22

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (SINGLE PACK & MULTIPACK ONLY)

184/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed

fluticasone furoate/vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate).

3. LIST OF EXCIPIENTS

Also contains lactose and magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation powder, pre-dispensed.

14 doses

30 doses

3 x 30 doses

1 inhaler of 14 doses

1 inhaler of 30 doses

Multipack: 90 (3 packs of 30) doses

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use,
ONCE DAILY

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

In use shelf-life: 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/886/004

EU/1/13/886/005

EU/1/13/886/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

relvar ellipta 184:22

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE OUTER CARTON (WITHOUT BLUE BOX- MULTIPACK ONLY)

92/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed

fluticasone furoate/vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate).

3. LIST OF EXCIPIENTS

Also contains lactose and magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

30 doses

1 inhaler of 30 doses.

Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use,
ONCE DAILY

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

In use shelf-life: 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/886/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

relvar ellipta 92:22

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE OUTER CARTON (WITHOUT BLUE BOX- MULTIPACK ONLY)

184/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed

fluticasone furoate /vilanterol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each delivered dose contains 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate).

3. LIST OF EXCIPIENTS

Also contains lactose and magnesium stearate.

4. PHARMACEUTICAL FORM AND CONTENTS

30 doses

1 inhaler of 30 doses.

Component of a multipack, not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use,
ONCE DAILY

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

In use shelf-life: 6 weeks.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Glaxo Group Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/886/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

relvar ellipta 184:22

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY LABEL

92/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed
fluticasone furoate /vilanterol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GSK Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open until ready to inhale.
In use shelf-life: 6 weeks.

14 doses

~~30 doses~~

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY LABEL

184/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT

Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed
fluticasone furoate/vilanterol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GSK Logo

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Do not open until ready to inhale.
In use shelf-life: 6 weeks.

14 doses
30 doses

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DEVICE LABEL

92/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Relvar Ellipta 92 micrograms/22 micrograms inhalation powder

fluticasone furoate/vilanterol

Inhalation use

2. EXPIRY DATE

EXP

In use shelf-life: 6 weeks

Discard by:

3. BATCH NUMBER

Lot

4. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

14 doses

30 doses

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

DEVICE LABEL

184/22 micrograms

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Relvar Ellipta 184 micrograms/22 micrograms inhalation powder

fluticasone furoate/vilanterol

Inhalation use

2. EXPIRY DATE

EXP

In use shelf-life: 6 weeks

Discard by:

3. BATCH NUMBER

Lot

4. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

14 doses

30 doses

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Relvar Ellipta 92 micrograms/22 micrograms inhalation powder, pre-dispensed Relvar Ellipta 184 micrograms/22 micrograms inhalation powder, pre-dispensed

Fluticasone furoate/vilanterol

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Relvar Ellipta is and what it is used for
2. What you need to know before you use Relvar Ellipta
3. How to use Relvar Ellipta
4. Possible side effects
5. How to store Relvar Ellipta
6. Contents of the pack and other information
Step-by-step instructions

1. What Relvar Ellipta is and what it is used for

Relvar Ellipta contains two active substances: fluticasone furoate and vilanterol. Two different strengths of Relvar Ellipta are available: fluticasone furoate 92 micrograms/vilanterol 22 micrograms and fluticasone furoate 184 micrograms/vilanterol 22 micrograms.

The 92/22 micrograms strength is used for the regular treatment of chronic obstructive pulmonary disease (**COPD**) in adults, and **asthma** in adults and adolescents 12 years and over.

The 184/22 micrograms strength is used to treat **asthma** in adults and adolescents aged 12 years and older.

Relvar Ellipta should be used every day and not only when you have breathing problems or other symptoms of COPD and asthma. It should not be used to relieve a sudden attack of breathlessness or wheezing. If you get this sort of attack you must use a quick-acting inhaler (such as salbutamol).

Fluticasone furoate belongs to a group of medicines called corticosteroids, often simply called steroids. Corticosteroids reduce inflammation. They reduce the swelling and irritation in the small air passages in the lungs and so gradually ease breathing problems. Corticosteroids also help to prevent attacks of asthma and aggravation of COPD.

Vilanterol belongs to a group of medicines called long acting bronchodilators. It relaxes the muscles of the small air passages in the lungs. This helps to open the airways and makes it easier for air to get in and out of the lungs. When it is taken regularly, it helps the small air passages to remain open.

When you take these two active substances together regularly, they will help to control your breathing difficulties more than either medicine alone.

Asthma is a serious, long term lung disease where the muscles surrounding the smaller airways become tight (*bronchoconstriction*) and swollen and irritated (*inflammation*). Symptoms come and go and include shortness of breath, wheezing, chest tightness and cough.

Chronic obstructive pulmonary disease (COPD) is a serious, long term lung disease where the airways become inflamed and thickened. Symptoms include shortness of breath, cough, chest discomfort and coughing up mucus. Relvar Ellipta has been shown to reduce flare-ups of COPD symptoms.

2. What you need to know before you use Relvar Ellipta

Do not use Relvar Ellipta

- if you are **allergic** to fluticasone furoate, vilanterol or any other ingredients of this medicine (listed in section 6).
- if you think the above applies to you, **don't use Relvar Ellipta** until you have checked with your doctor.

Take special care with Relvar Ellipta

Talk to your doctor before you use Relvar Ellipta:

- if you have **liver disease**, as you may be more likely to have side effects. If you have moderate or severe liver disease, your doctor will limit your dose to the lower strength of Relvar Ellipta (92/22 micrograms once daily).
- if you have **heart problems** or **high blood pressure**.
- if you have tuberculosis (TB) of the lung, or any long standing or untreated infections.
- if you have a history of diabetes.
- if you have **thyroid gland problems**.
- if you have **low potassium** in your blood.

Check with your doctor before you use this medicine if you think any of these applies to you.

Immediate breathing difficulties

If your breathing or wheezing gets worse straight after using Relvar Ellipta, **stop using it** and **get medical help** immediately.

Infection of the lung

If you are using this medicine for COPD you may be at an increased risk of developing an infection of the lungs known as pneumonia. See section 4 'Possible side effects' for information on symptoms to look out for while you are using this medicine. Tell your doctor as soon as possible if you develop any of these symptoms.

Children and adolescents

This medicine is not recommended in children under the age of 12 years for the treatment of asthma, or in children and adolescents of any age for the treatment of COPD.

Other medicines and Relvar Ellipta

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines may affect how this medicine works, or make it more likely that you will have side effects. These include:

- beta-blockers, such as metoprolol, used to treat **high blood pressure** or **a heart condition**.
- ketoconazole, to treat **fungal infections**.

- ritonavir, to treat **HIV infections**.
- long-acting beta₂-adrenergic agonists, such as salmeterol

Tell your doctor or pharmacist if you are taking any of these medicines.

Pregnancy

Relvar Ellipta should only be considered for pregnant women if the expected benefits outweigh the risks.

If you are pregnant, if you think you may be pregnant, or if you are planning to have a baby, ask your doctor for advice before taking this medicine.

Breast-feeding

It is not known whether this medicine can pass into breast milk. Therefore a risk to breastfed infants cannot be ruled out.

If you are breast-feeding, **check with your doctor** before you take Relvar Ellipta.

Driving and using machines

This medicine is unlikely to affect your ability to drive or use machines.

Relvar Ellipta contains lactose

If you have been diagnosed with an intolerance to some sugars, or to milk protein, talk to your doctor before you use this medicine.

3. How to use Relvar Ellipta

Always use this medicine exactly as your doctor has told you to. Check with your doctor, nurse or pharmacist if you are not sure.

How much to use

Asthma

The recommended dose to treat asthma is one inhalation (92 micrograms of fluticasone furoate and 22 micrograms of vilanterol) once daily at the same time each day.

If you have severe asthma, your doctor may decide that you should use one inhalation of the higher strength inhaler (184 micrograms fluticasone furoate and 22 micrograms of vilanterol). This dose is also used once daily at the same time each day.

COPD

The recommended dose to treat COPD is one inhalation (92 micrograms of fluticasone furoate and 22 micrograms of vilanterol) once daily at the same time each day.

The higher strength of Relvar Ellipta is not suitable for the treatment of COPD.

Use Relvar Ellipta at the same time each day as it is effective over 24 hours

It is very important that you use this medicine every day, as instructed by your doctor. This will help to keep you free of symptoms throughout the day and night.

Relvar Ellipta should not be used to relieve a sudden attack of breathlessness or wheezing. If you get this sort of attack you must use a quick-acting inhaler (such as salbutamol).

If you feel you are getting breathless or wheezy more often than normal, or if you are using your quick-acting inhaler more than usual, see your doctor.

How to use Relvar Ellipta

See 'Step-by-step instructions' after section 6 of this leaflet for full information.

You do not need to prepare Relvar Ellipta in any special way, not even the first time you use it.

If your symptoms do not improve

If your symptoms (breathlessness, wheezing, cough) do not improve or get worse, or if you are using your quick-acting inhaler more often

contact your doctor as soon as possible.

If you use more Relvar Ellipta than you should

If you accidentally take more Relvar Ellipta than your doctor has instructed, talk to your doctor or pharmacist. You may notice that your heart is beating faster than usual, you feel shaky or have a headache.

If you have used more than instructed for a long period of time, it is particularly important that you ask your doctor or pharmacist for advice. This is because larger doses of Relvar Ellipta may reduce the amount of steroid hormones produced naturally by your body.

If you forget to use Relvar Ellipta

Do not take a double dose to make up for a forgotten dose. Just take your next dose at the usual time.

If you become wheezy or breathless, or develop any other symptoms of an asthma attack, **use your quick-acting inhaler** (e.g. salbutamol), then seek medical advice.

Do not stop using Relvar Ellipta without advice

Use this medicine for as long as your doctor recommends. It will only be effective as long as you are using it. Do not stop unless your doctor advises you to, even if you feel better.

If you have further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic Reactions

Allergic reactions to Relvar Ellipta are rare (they affect less than 1 person in 1000).

If you have any of the following symptoms after taking Relvar Ellipta **stop taking this medicine and tell your doctor immediately.**

- skin rash (*hives*) or redness
- swelling, sometimes of the face or mouth (*angioedema*)
- becoming very wheezy, coughing or having difficulty in breathing
- suddenly feeling weak or light headed (which may lead to collapse or loss of consciousness)

Immediate breathing difficulties

If your breathing or wheezing gets worse straight after using this medicine, **stop using it and get medical help** immediately.

Pneumonia (infection of the lung) (common side effect)

Tell your doctor if you have any of the following while taking Relvar Ellipta – they could be symptoms of a lung infection:

- fever or chills
- increased mucus production, change in mucus colour
- increased cough or increased breathing difficulties

Other side effects include:

Very common side effects

These may affect **more than 1 in 10** people:

- headache
- common cold

Common side effects

These may affect **up to 1 in 10** people:

- sore, raised patches in the mouth or throat caused by a fungal infection (*candidiasis*). Rinsing your mouth out with water immediately after using Relvar Ellipta may help stop this side effect developing.
- inflammation of the lungs (*bronchitis*)
- infection of the nose sinuses or throat
- flu (*influenza*)
- pain and irritation in the back of the mouth and throat
- inflammation of the sinuses
- itchy, runny or blocked nose
- cough
- voice disorders
- weakening of the bones, leading to fractures
- stomach pain
- back pain
- high temperature (*fever*)
- joint pain
- muscle spasms

Uncommon side effect

This may affect **up to 1 in 100** people:

- irregular heartbeat

Rare side effects

These may affect up to **1 in 1,000** people:

- allergic reactions
- heart beating faster (*tachycardia*)
- awareness of heart beat (*palpitations*)
- tremor
- anxiety

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Relvar Ellipta

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

Store in the original package in order to protect from moisture and do not open the foil lid tray until ready to inhale. Once the tray is opened, the inhaler can be used for up to 6 weeks, starting from the date of opening the tray. Write the date the inhaler should be discarded on the label in the space provided. The date should be added as soon as the inhaler has been removed from the tray.

If you store in a refrigerator, **allow the inhaler to return to room temperature for at least an hour** before use.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Relvar Ellipta contains

- The active substances are fluticasone furoate and vilanterol. Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 or 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenate).
- The other ingredients are lactose monohydrate and magnesium stearate.

What Relvar Ellipta looks like and contents of the pack

Relvar Ellipta is a white powder. The Ellipta device itself is a light grey inhaler with a yellow mouthpiece cover and a dose counter. It is packaged in a foil laminate tray with a peelable foil lid. The tray contains a desiccant sachet, to reduce moisture in the packaging. Once you have opened the lid of the tray, throw the desiccant away – do not eat or inhale it. The device does not need to be stored in the foil laminate tray once it has been opened.

The inhaler contains two aluminium foil laminate strips of 14 or 30 doses. Multipacks contain 3 x 30 dose inhalers.

Step by step instructions

What is the Ellipta inhaler?

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

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 tray, it will be in the ‘closed’ position. **Do not open it until you are ready to inhale a dose of medicine.** When the tray is opened, write the “Discard by” date on the inhaler label in the space provided. The “Discard by” date is 6 weeks from the date you opened the tray. After this date the inhaler should no longer be used. The tray can be discarded after first opening.

1. 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.

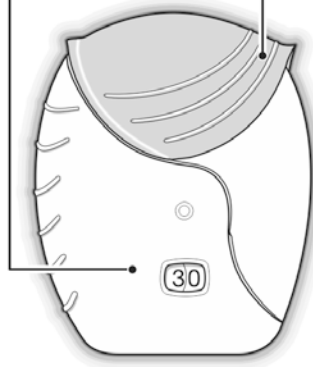
When fewer than 10 doses are left, half of the dose counter shows red.

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

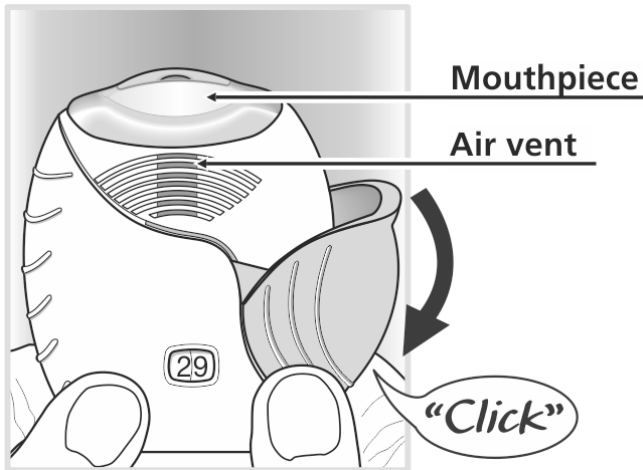
Each time you open this, you prepare one dose of medicine.



2. Prepare a dose

Wait to open the cover until you are ready to take your dose. Do not shake the inhaler.

- **Slide the cover down until you hear a “click”.**

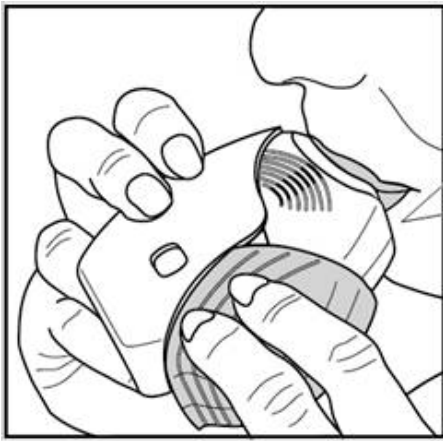


Your medicine is now ready to be inhaled.
The dose counter counts down by **1** to confirm.

- If the dose counter does not count down as you hear the “click”, the inhaler will not deliver medicine. Take it back to your pharmacist for advice.

3. Inhale your medicine

- **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.



Your lips fit over the contoured shape of the mouthpiece for inhaling.
Do not block the air vent with your fingers.

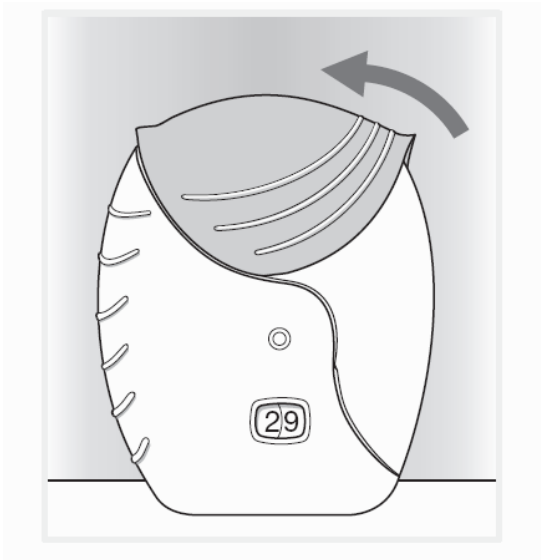
- **Take one long, steady, deep breath in. Hold this breath for as long as possible (at least 3-4 seconds).**
- **Remove the inhaler from your mouth.**
- **Breathe out slowly and gently.**

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

4. 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.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Glaxo Group Limited,

980 Great West Road,
Brentford,
Middlesex TW8 9GS.
United Kingdom.

Manufacturer:

Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations),
Priory Street,
Ware,
Hertfordshire, SG12 0DJ
United Kingdom

Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations),
Harmire Road,
Barnard Castle,
County Durham, DL12 8DT
United Kingdom.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Tél/Tel: + 32 (0) 10 85 52 00

България

ГлаксоСмитКлайн ЕООД
Тел.: + 359 2 953 10 34

Česká republika

GlaxoSmithKline s.r.o.
Tel: + 420 222 001 111
cz.info@gsk.com

Danmark

GlaxoSmithKline Pharma A/S
Tlf: + 45 36 35 91 00
dk-info@gsk.com

Deutschland

GlaxoSmithKline GmbH & Co. KG
Tel.: + 49 (0)89 36044 8701
produkt.info@gsk.com

Eesti

GlaxoSmithKline Eesti OÜ
Tel: + 372 6676 900
estonia@gsk.com

Ελλάδα

GlaxoSmithKline A.E.B.E.
Τηλ: + 30 210 68 82 100

Lietuva

GlaxoSmithKline Lietuva UAB
Tel: + 370 5 264 90 00
info.lt@gsk.com

Luxembourg/Luxemburg

GlaxoSmithKline Pharmaceuticals s.a./n.v.
Belgique/Belgien
Tél/Tel: + 32 (0) 10 85 52 00

Magyarország

GlaxoSmithKline Kft.
Tel.: + 36 1 225 5300

Malta

GlaxoSmithKline Malta
Tel: + 356 21 238131

Nederland

GlaxoSmithKline BV
Tel: + 31 (0)30 6938100
nlinfo@gsk.com

Norge

GlaxoSmithKline AS
Tlf: + 47 22 70 20 00
firmapost@gsk.no

Österreich

GlaxoSmithKline Pharma GmbH
Tel: + 43 (0)1 97075 0
at.info@gsk.com

España

GlaxoSmithKline, S.A.
Tel: + 34 902 202 700
es-ci@gsk.com

France

Laboratoire GlaxoSmithKline
Tél.: + 33 (0)1 39 17 84 44
diam@gsk.com

Hrvatska

GlaxoSmithKline d.o.o.
Tel: + 385 1 6051 999

Ireland

GlaxoSmithKline (Ireland) Limited
Tel: + 353 (0)1 4955000

Ísland

Vistor hf.
Sími: + 354 535 7000

Italia

GlaxoSmithKline S.p.A.
Tel: + 39 (0)45 9218 111

Κύπρος

GlaxoSmithKline (Cyprus) Ltd
Τηλ: + 357 22 39 70 00
gskcyprus@gsk.com

Latvija

GlaxoSmithKline Latvia SIA
Tel: + 371 67312687
lv-epasts@gsk.com

Polska

GSK Services Sp. z o.o.
Tel.: + 48 (0)22 576 9000

Portugal

GlaxoSmithKline – Produtos Farmacêuticos, Lda.
Tel: + 351 21 412 95 00
FI.PT@gsk.com

România

GlaxoSmithKline (GSK) S.R.L.
Tel: + 4021 3028 208

Slovenija

GlaxoSmithKline d.o.o.
Tel: + 386 (0)1 280 25 00
medical.x.si@gsk.com

Slovenská republika

GlaxoSmithKline Slovakia s. r. o.
Tel: + 421 (0)2 48 26 11 11
recepacia.sk@gsk.com

Suomi/Finland

GlaxoSmithKline Oy
Puh/Tel: + 358 (0)10 30 30 30
Finland.tuoteinfo@gsk.com

Sverige

GlaxoSmithKline AB
Tel: + 46 (0)8 638 93 00
info.produkt@gsk.com

United Kingdom

GlaxoSmithKline UK
Tel: + 44 (0)800 221441
customercontactuk@gsk.com

This leaflet was last revised in <{MM/YYYY}>

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.

----->

