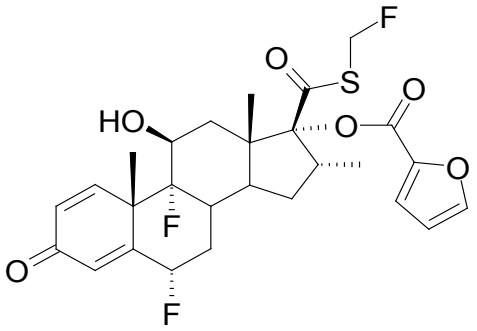
BREO™ ELLIPTA®

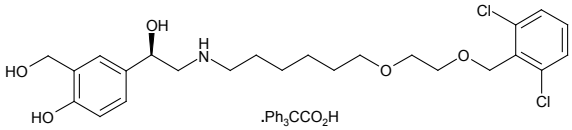
PRODUCT INFORMATION

NAME OF THE MEDICINE Fluticasone furoate/vilanterol trifenatate

Structure of fluticasone furoate



Structure of vilanterol trifenatate



Chemical Name: The chemical name of fluticasone furoate is androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-, S-(fluoromethyl) ester, (6α,11β,16α,17α)- (9CI)

The chemical name of vilanterol trifenatate is benzeneacetic acid, α,α-diphenyl-, compd. with (α1R)-α1-[[[6-[2-[(2,6-dichlorophenyl)methoxy]ethoxy] hexyl]amino]methyl]-4-hydroxy-1,3-benzene dimethanol (1:1)

Molecular Formula: Fluticasone furoate: $C_{27}H_{29}F_3O_6S$

Vilanterol trifenatate: $C_{24}H_{33}Cl_2NO_5.C_{20}H_{16}O_2$

CAS Number: Fluticasone furoate: 397864-44-7

Vilanterol trifenatate: 503070-58-4

DESCRIPTION

Fluticasone furoate is practically insoluble or insoluble in water, and slightly soluble in acetone, dimethylsulphoxide and ethanol.

Vilanterol trifenatate is practically insoluble or insoluble in water and slightly soluble in methanol, ethanol, acetonitrile and propan-2-ol.

Breo Ellipta is a moulded plastic inhaler with a light grey body, a pale blue mouthpiece cover and a dose counter, packed in a foil tray which contains a desiccant packet. The tray is sealed with a peelable lid. The inhaler contains two strips of either 30 or 14 regularly distributed blisters, each containing a white powder.

Breo Ellipta also contains the excipients lactose monohydrate (which contains milk protein) and magnesium stearate.

PHARMACOLOGY

Pharmacodynamics:

Fluticasone furoate and vilanterol represent two classes of medications (a synthetic corticosteroid and a selective, long-acting $beta_2$-receptor agonist).

Fluticasone furoate

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

Vilanterol trifenatate

Vilanterol trifenatate is a selective long-acting, $beta_2$-adrenergic agonist (LABA).

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including vilanterol trifenatate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the $beta_2$-receptor gene, increasing receptor number 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 have also shown the synergy between corticosteroids and LABAs to occur at clinical doses of the drugs in patients with COPD.

Pharmacokinetics:

Absorption

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

Distribution

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

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

Fluticasone furoate and vilanterol are substrates for P-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.

Metabolism

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

Fluticasone furoate is primarily metabolised through hydrolysis of the S-fluoromethyl carbothioate group to metabolites with significantly reduced corticosteroid activity.

Vilanterol is primarily metabolised by O-dealkylation to a range of metabolites with significantly reduced β_1- and β_2-agonist activity.

A repeat dose CYP3A4 drug interaction study was performed in healthy subjects with the fluticasone furoate/vilanterol combination (200/25) and the strong CYP3A4 inhibitor ketoconazole (400mg). Co-administration increased mean fluticasone furoate $AUC_{(0-24)}$ and C_{max} by 36% and 33%, respectively. The increase in fluticasone furoate exposure was associated with a 27% reduction in 0-24 h weighted mean serum cortisol. Co-administration increased mean vilanterol $AUC_{(0-t)}$ and C_{max} 65% and 22%, respectively. The increase in vilanterol exposure was not associated with an increase in beta-agonist related systemic effects on heart rate, blood potassium or QTcF interval.

Excretion

Following oral administration fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with <1% of the recovered radioactive dose eliminated in the urine. The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of fluticasone furoate/vilanterol was, on average, 24 hours.

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

Special Patient Populations

Population PK meta-analyses for fluticasone furoate and vilanterol were conducted in phase III studies in subjects with asthma or COPD. The impact of demographic covariates (age, gender, weight, BMI, racial group, ethnicity) on the pharmacokinetics of fluticasone furoate and vilanterol were evaluated as part of the population pharmacokinetic analysis.

Race

In elderly subjects with asthma or COPD estimates of fluticasone furoate $AUC_{(0-24)}$ for East Asian, Japanese and South Asian subjects (12-14% subjects) were up to 53% higher on average compared with Caucasian subjects. However, there was no evidence for the higher systemic exposure in these populations to be associated with greater effect on 24 hour urinary cortisol excretion. There was no effect of race on pharmacokinetic parameter estimates of vilanterol in subjects with COPD.

In subjects with asthma, on average, vilanterol C_{max} is estimated to be 220 to 287% higher and $AUC_{(0-24)}$ comparable for those subjects from an Asian heritage compared with subjects from other racial groups. However, there was no evidence that this higher vilanterol C_{max} resulted in clinically significant effects on heart rate.

Children

Breo Ellipta should not be used in children (i.e. patients younger than 12 years of age).

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

Elderly

The effects of age on the pharmacokinetics of fluticasone furoate and vilanterol were determined in phase III studies in COPD and asthma.

There was no evidence for age (12-84) to affect the PK of fluticasone furoate or vilanterol in subjects with asthma.

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

Renal Impairment

A clinical pharmacology study of fluticasone furoate/vilanterol showed that severe renal impairment (creatinine clearance <30 mL/min) did not result in significantly greater exposure to fluticasone furoate or vilanterol or more marked corticosteroid or $beta_2$-agonist

systemic effects compared with healthy subjects. No dose adjustment is required for patients with renal impairment.

The effects of haemodialysis have not been studied.

Hepatic Impairment

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was an increase in fluticasone furoate systemic exposure (up to three-fold as measured by $AUC_{(0–24)}$) in subjects with hepatic impairment (Child-Pugh A, B or C) compared with healthy subjects. The increase in fluticasone furoate systemic exposure (fluticasone furoate/vilanterol 200/25 micrograms) in subjects with moderate hepatic impairment (Child-Pugh B) was associated with an average 34% reduction in serum cortisol compared with healthy subjects. In subjects with severe hepatic impairment (Child-Pugh C) that received a lower dose of 100/12.5 micrograms there was no reduction in serum cortisol. For patients with moderate or severe hepatic impairment the maximum dose is 100/25 micrograms (see Dosage and Administration).

Following repeat dosing of fluticasone furoate/vilanterol for 7 days, there was no significant increase in systemic exposure to vilanterol (C_{max} and AUC) in subjects with mild, moderate, or severe hepatic impairment (Child-Pugh A, B or C).

There were no clinically relevant effects of the fluticasone furoate/vilanterol combination on beta-adrenergic systemic effects (heart rate or serum potassium) in subjects with mild or moderate hepatic impairment (vilanterol, 25 micrograms) or with severe hepatic impairment (vilanterol, 12.5 micrograms) compared with healthy subjects.

Gender, Weight and BMI

There was no evidence for gender, weight or BMI to influence the pharmacokinetics of fluticasone furoate based on a population pharmacokinetic analysis of phase III data in 1213 subjects with asthma (712 females) and 1225 subjects with COPD (392 females).

There was no evidence for gender, weight or BMI to influence the pharmacokinetics of vilanterol based on a population pharmacokinetic analysis in 856 subjects with asthma (500 females) and 1091 subjects with COPD (340 females).

No dosage adjustment is necessary based on gender, weight or body mass index (BMI).

CLINICAL TRIALS

Asthma

The safety and efficacy of fluticasone furoate (FF) and vilanterol (VI) in the treatment of asthma has been evaluated in 3 randomised, double-blind clinical trials of between 12 to 76 weeks in duration (HZA106827, HZA106829 and HZA106837) involving 3210 patients 12 years of age and older with persistent asthma.

All subjects were using an ICS (Inhaled Corticosteroid) with or without LABA for at least 12 weeks prior to Visit 1. In HZA106837 all patients had at least one exacerbation that required treatment with oral corticosteroids in the year prior to Visit 1. HZA106827 was 12 weeks in duration and evaluated the efficacy of fluticasone furoate/vilanterol 100 micrograms/25 micrograms [n=201] and FF (fluticasone furoate) 100 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 200 micrograms/25 micrograms [n=197] and FF 200 micrograms [n=194]) both administered once daily compared with fluticasone propionate (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) FEV_1 at the end of the treatment period in all subjects and weighted mean serial FEV_1 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 below:

Table 1 ***Summary of Data from Studies HZA106829 and HZA106827***

Study No.	HZA106829		HZA106827	
Treatment Dose of FF/VI*(micrograms)	FF/VI 200/25 Once Daily vs FF 200 Once Daily	FF/VI 200/25 Once Daily vs FP 500 Twice Daily	FF/VI 100/25 Once Daily vs FF 100 Once Daily	FF/VI/100/25 Once Daily vs placebo Once Daily
Change from Baseline in Trough FEV_1 Last Observation Carried Forward (LOCF)				
Treatment difference P value (95% CI)	193mL p<0.001 (108, 277)	210mL p<0.001 (127, 294)	36mL p=0.405 (-48, 120)	172mL p<0.001 (87, 258)
Weighted Mean Serial FEV_1 over 0-24 hours post-dose				
Treatment difference P value (95% CI)	136mL p=0.048 (1, 270)	206mL p=0.003 (73, 339)	116mL p=0.06 (-5, 236)	302mL p<0.001 (178, 426)
Change from Baseline in Percentage of Rescue-Free 24-hour Periods				
Treatment difference P value (95% CI)	11.7% p<0.001 (4.9, 18.4)	6.3% p=0.067 (-0.4, 13.1)	10.6% p<0.001 (4.3, 16.8)	19.3% p<0.001 (13.0, 25.6)
Change from Baseline in Percentage of Symptom-Free 24-hour Periods				
Treatment difference P value (95% CI)	8.4% p=0.010 (2.0, 14.8)	4.9% p=0.137 (-1.6, 11.3)	12.1% p<0.001 (6.2, 18.1)	18.0% p<0.001 (12.0, 23.9)
Change from Baseline in AM Peak Expiratory Flow				
Treatment difference P value (95% CI)	33.5L/min p<0.001 (25.3, 41.7)	32.9L/min p<0.001 (24.8, 41.1)	14.6L/min p<0.001 (7.9, 21.3)	33.3L/min p<0.001 (26.5, 40.0)
Change from Baseline in PM Peak Expiratory Flow				
Treatment difference P value (95% CI)	30.7L/min p<0.001 (22.5, 38.9)	26.2L/min p<0.001 18.0, 34.3)	12.3L/min p<0.001 (5.8, 18.8)	28.2L/min p<0.001 (21.7, 34.8)

**FF/VI = fluticasone furoate/vilanterol*

In Study HZA106829, FF 200 once daily was non-inferior to FP 500 twice daily for the primary endpoint of trough FEV1 using a predefined non inferiority margin of -125 mL (treatment difference of 18 mL [95% CI: -66, 102]).

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

100 micrograms/25 micrograms [n=1009] or FF 100 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 FEV_1 was also evaluated as a secondary endpoint.

In HZA106837 the risk of experiencing a severe asthma exacerbation in patients receiving fluticasone furoate/vilanterol 100 micrograms/25 micrograms was reduced by 20% compared with FF 100 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 100 group (approximately 1 in every 5 years) and 0.14 in the fluticasone furoate/vilanterol 100 micrograms/25 micrograms group (approximately 1 in every 7 years). The ratio of the exacerbation rate for fluticasone furoate/vilanterol 100 micrograms/25 micrograms versus FF 100 was 0.755 (95% CI 0.603, 0.945). This represents a 25% reduction in the rate of severe asthma exacerbations for subjects treated with fluticasone furoate/vilanterol 100 micrograms/25 micrograms compared with FF 100 (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 100 micrograms/25 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV_1 at weeks 12, 36 and 52 and Endpoint compared with FF 100 micrograms (p<0.001 95% CI 52, 126mL at Endpoint). Forty four percent of patients in the fluticasone furoate/vilanterol 100 micrograms/25 group were well controlled (ACQ7 ≤0.75) at end of treatment compared to 36% of subjects in the FF 100 microgram group (p<0.001 95% CI 1.23, 1.82).

Studies versus salmeterol/fluticasone propionate combinations

In a 24 week study (HZA113091) in adult and adolescent patients with persistent asthma both fluticasone furoate/vilanterol 100 micrograms/25 micrograms given once daily in the evening and FP/salmeterol 250/50 micrograms given twice daily demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV_1 of 341 mL (fluticasone furoate/vilanterol) and 377 mL (FP/salmeterol) 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).

Fluticasone furoate monotherapy

A 24 week randomised, double-blind placebo controlled study (FFA112059) evaluated the safety and efficacy of FF 100 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) FEV_1 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 100 and FP increased trough FEV_1 by 146 mL (95% CI 36, 257mL, p=0.009) and 145 mL (95% CI 33, 257mL, 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 100 micrograms/25 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 100/25 micrograms, FF 100 micrograms, VI (vilanterol) 25 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 FEV_1 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 100 micrograms/25 micrograms compared with FF 100 micrograms or vilanterol 25 micrograms alone. Both fluticasone furoate/vilanterol (100 micrograms/25 micrograms) and FF 100 micrograms virtually abolished the late asthmatic response compared with vilanterol alone. Fluticasone furoate/vilanterol 100/25 micrograms provided significantly greater protection against allergen-induced bronchial hyper-reactivity compared with monotherapies FF and VI as assessed on Day 22 by methacholine challenge.

Chronic Obstructive Pulmonary Disease

The COPD clinical development programme included a 12-week (HZC113107), two 6-month (HZC112206, HZC112207) and two one-year randomised controlled studies (HZC102970, HZC102871) 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 50 micrograms/25 micrograms [n=206] and fluticasone furoate/vilanterol 100 micrograms/25 micrograms [n=206] compared with FF 100 micrograms [n=206], vilanterol 25 micrograms [n=205] and placebo (n = 207), all administered once daily. HZC112207 evaluated the efficacy of fluticasone furoate/vilanterol 100 micrograms/25 micrograms [n=204] and fluticasone furoate/vilanterol 200 micrograms/25 micrograms [n=205] compared with FF 100 micrograms [n=204], 200 micrograms [n=203] and vilanterol 25 micrograms [n=203] and placebo [n = 205], all administered once daily.

All patients were required to have a smoking history of at least 10 pack years; a post-salbutamol FEV_1/FVC ratio less than or equal to 0.70; post-salbutamol FEV_1 less than or equal to 70% predicted and have a Modified Medical Research Council (mMRC) dyspnea score $\geq$2 (scale 0-4) at screening. At screening, the mean pre-bronchodilator FEV_1 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 FEV_1 from zero to 4 hours post-dose at Day 168 and change from baseline in pre-dose trough FEV_1 at Day 169.

In an integrated analysis of both studies, fluticasone furoate/vilanterol 100 micrograms/25 micrograms showed clinically meaningful improvements in lung function. At Day 169 fluticasone furoate/vilanterol 100 micrograms/25 micrograms and vilanterol increased adjusted mean trough FEV_1 by 129mL (95% CI: 91, 167mL, $p<0.001$)

and 83 mL (95% CI: 46, 121mL, p<0.001) respectively compared to placebo. Fluticasone furoate/vilanterol 100 micrograms/25 micrograms increased trough FEV_1 by 46 mL compared to vilanterol (95% CI: 8, 83mL, p= 0.017). At Day 168 fluticasone furoate/vilanterol 100 micrograms/25 micrograms and vilanterol increased adjusted mean weighted mean FEV_1 over 0-4 hours by 193mL (95% CI: 156, 230mL, p<0.001) and 145 mL (95% CI: 108, 181mL, p<0.001) respectively compared to placebo. Fluticasone furoate/vilanterol 100/25 micrograms increased adjusted mean weighted mean FEV_1 over 0-4 hours by 148 ml compared to FF alone (95% CI: 112, 184mL, p< 0.001).

In both the HZC112206 and HZC112207 studies, at day 168, differences were seen in the adjusted mean change from baseline CRQ-SAS dyspnoea scores between the fluticasone furoate/vilanterol 100 micrograms/25 micrograms and placebo groups (HZC112206: 0.30, (95% CI 0.06,0.54 p=0.014); HZC112207: 0.24, (95% CI 0.02,0.46 p=0.029) and between the fluticasone furoate/vilanterol 100 micrograms/25 micrograms and FF 100 microgram groups (HZC112206: 0.24, (95% CI 0.01,0.48, p=0.044); HZC112207: 0.36, (95% CI (0.14,0.57), p=0.001). For all the other pair-wise treatment comparisons at Day 168 for the CRQ-SAS dyspnoea score, the p-value was >0.05. In both studies, none of the treatment comparisons at Day 168 achieved a minimal clinically important difference (>0.5 point improvement) in mean CRQ-SAS Dyspnoea Domain scores. Patients treated with fluticasone furoate/vilanterol 100 micrograms/25 micrograms also had significantly less cough and sputum, required significantly less rescue medication as measured by number of occasions of rescue salbutamol use (per 24 hour period) and number of night time awakenings requiring salbutamol (per 24 hour period) compared to placebo.

12 month studies

Studies HZC102970 and HZC102871 were 52 week randomised, double-blind, parallel-group, studies comparing the effect of fluticasone furoate/vilanterol
200 micrograms/25 micrograms, fluticasone furoate/vilanterol
100 micrograms/25 micrograms, fluticasone furoate/vilanterol
50 micrograms/25 micrograms with vilanterol 25 micrograms, all administered once daily, on the annual rate of moderate/severe exacerbations in subjects with COPD with a smoking history of at least 10 pack years and a post-salbutamol FEV_1/FVC ratio less than or equal to 0.70 and post-salbutamol FEV_1 less than or equal to 70% predicted and documented history of ≥ 1 COPD exacerbation that required antibiotics and/or oral corticosteroids or hospitalisation in the 12 months prior to visit 1. The primary endpoint was the annual rate of moderate and severe exacerbations. 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 FP/salmeterol 250/50 twice daily to standardise COPD pharmacotherapy and stabilise disease prior to randomisation to blinded study medication for 52 weeks. Prior to run-in, subjects discontinued use of previous COPD medications except short-acting bronchodilators. The use of concurrent inhaled long-acting bronchodilators ($beta_2$-agonist and anticholinergic), ipratropium/salbutamol combination products, oral $beta_2$-agonists, and theophylline preparations were not allowed during the treatment period. Oral corticosteroids and antibiotics were allowed for the acute treatment of COPD exacerbations with specific guidelines for use. Subjects used salbutamol on an as-needed basis throughout the studies.

The results of an integrated analysis showed that treatment with fluticasone furoate/vilanterol 100/25 micrograms once daily resulted in a 27% reduction in the annual rate of moderate or severe COPD exacerbations compared with vilanterol (95% CI: 0.63, 0.84 (p<0.001). Similar reductions in the time to first exacerbation and exacerbations

requiring systemic corticosteroid use were observed with fluticasone furoate/vilanterol 100/25 micrograms once daily.

Table 2 Analysis of Exacerbation Rates following 12 months of treatment

Endpoint	HZC102970		HZC102871		HZC102970 and HZC102871 integrated	
	Vilanterol (n=409)	FF/VI 100/25 (n=403)	Vilanterol (n=409)	FF/VI 100/25 (n=403)	Vilanterol (n=818)	FF/VI 100/25 (n=806)
Moderate and severe exacerbations						
Adjusted mean annual rate	1.14	0.90	1.05	0.70	1.11	0.81
Ratio vs VI 95% CI p-value % reduction 95% CI		0.79 (0.64,0.97) 0.024 21 (3, 36)		0.66 (0.54, 0.81) <0.001 34 (19,46)		0.73 (0.63, 0.84) <0.001 27 (16, 37)
Time to first exacerbation: Hazard ratio (95% CI) % risk reduction p-value		 0.80 (0.66, 0.99) 20 0.036		 0.72 (0.59, 0.89) 28 0.002		 0.76 (0.66, 0.88) 24 p<0.001
Exacerbations requiring systemic/oral corticosteroids						
Annual rate	0.86	0.66	0.84	0.52	0.87	0.61
Ratio vs VI 95% CI p-value % reduction 95% CI		0.77 (0.60,0.99) 0.041 23 (1, 40)		0.62 (0.49, 0.78) <0.001 38 (22, 51)		0.70 (0.59, 0.83) <0.001 30 (17, 41)

In an integrated analysis of HZC102970 and HZC102871 at week 52, an improvement was seen when comparing the fluticasone furoate/vilanterol 100 micrograms/25 micrograms vs. vilanterol 25 micrograms in adjusted mean trough FEV_1 (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 in the cardiovascular history/risk factors subgroup 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 100 micrograms/25 micrograms resulted in a significantly lower annual rate of moderate/severe COPD exacerbations compared with vilanterol (adjusted mean annual rates of 0.83 and 1.18 respectively, 30% reduction (95% CI 16, 42%, p<0.001). Improvements were also seen in this subgroup at week 52 when comparing the

fluticasone furoate/vilanterol 100 micrograms/25 micrograms vs. vilanterol 25 micrograms in adjusted mean trough FEV_1 (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 100 micrograms/25 micrograms given once daily in the morning and FP/salmeterol 500/50 micrograms given twice daily, demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV_1 of 130 mL (fluticasone furoate/vilanterol) and 108 mL (FP/salmeterol) 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). A clinically meaningful mean improvement was achieved for mean change from baseline in SGRQ Total Score after 12 weeks of treatment for the fluticasone furoate/vilanterol 100 micrograms/25 micrograms once daily treatment group (-4.78) but not for the FP/salmeterol 500/50 twice daily treatment group (-3.29). The adjusted mean treatment difference was -1.50 (p=0.215. 95% CI (-3.86, 0.87).

INDICATIONS

COPD

Breo Ellipta is indicated for symptomatic treatment of patients with COPD with a FEV_1 <70% predicted normal (post-bronchodilator) in patients with an exacerbation history despite regular bronchodilator therapy.

Breo Ellipta is not indicated for the initiation of bronchodilator therapy in COPD.

Asthma

Breo Ellipta is indicated in the regular treatment of moderate to severe asthma in patients who require a medium to high dose inhaled corticosteroid combined with a long-acting beta-2-agonist.

Vilanterol, an active ingredient in Breo Ellipta, is a long-acting beta-2-agonist (LABA). A class effect of all LABAs can be an increased risk of asthma death (see Precautions).

CONTRAINDICATIONS

Fluticasone furoate/vilanterol is contraindicated in patients with severe milk-protein allergy or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol or any of the excipients.

PRECAUTIONS

Precautions for use

Vilanterol, an active ingredient in Breo Ellipta, is a long-acting beta-2-agonist (LABA). Limited post-marketing data are available for vilanterol; however, post-marketing data for other LABAs show that LABAs can be associated with an increased risk of asthma death. This is considered a class effect of all LABAs.

Fluticasone furoate 100 micrograms is a medium dose of inhaled corticosteroid and fluticasone furoate 200 micrograms is a high dose of inhaled corticosteroid. Medium to high doses of inhaled corticosteroids may cause systemic effects. These include growth

retardation in adolescents (see below under Precautions subsection 'Systemic corticosteroid effects').

Breo Ellipta should only be used for patients not adequately controlled on a long-term, asthma control medication, such as an inhaled corticosteroid. Patients should be assessed at regular intervals. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained. In patients whose asthma is well controlled and stable with the lowest strength of Breo Ellipta, the next step should consider cessation of Breo Ellipta and transfer to maintenance therapy with an inhaled corticosteroid alone.

Breo Ellipta should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using Breo Ellipta should not use another medicine containing a LABA (e.g., salmeterol, eformoterol, indacaterol) for any reason.

Breo Ellipta 200/25 micrograms is not recommended for patients with COPD (see Dosage and Administration).

Deterioration of disease

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

Patients with asthma or COPD should have a personal action plan designed in association with their general practitioner. Patients should not stop therapy with Breo Ellipta, in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

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

Paradoxical bronchospasm

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

Cardiovascular effects

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic drugs, including fluticasone furoate/vilanterol. In addition, $beta_2$-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Therefore Breo Ellipta should be used with caution in patients with severe cardiovascular disease.

Patients with hepatic impairment

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

Systemic corticosteroid effects

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

Inhaled corticosteroids should be used with caution in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Pneumonia

An increase in pneumonia has been observed in patients with COPD receiving fluticasone furoate/vilanterol. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences these pneumonia events were fatal (see Clinical Trials and Adverse Effects). Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of such infections overlap with the symptoms of COPD exacerbations. Risk factors for pneumonia in patients with COPD receiving fluticasone furoate/vilanterol include current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with a (forced expiratory volume) FEV_1<50% predicted. These factors should be considered when Breo Ellipta is prescribed and treatment should be re-evaluated if pneumonia occurs.

Breo Ellipta 200/25 micrograms is not indicated for patients with COPD. There is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions with fluticasone furoate/vilanterol 200/25 micrograms (see Adverse Effects).

The incidence of pneumonia in patients with asthma was uncommon at the higher dose. The incidence of pneumonia in patients with asthma taking fluticasone furoate/vilanterol 200/25 micrograms was numerically higher compared with those receiving fluticasone furoate/vilanterol 100/25 or placebo (see Adverse Effects). No risk factors were identified.

Sensitivity to sympathomimetic amines

Breo Ellipta, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or hyperthyroidism and in those who are unusually responsive to sympathomimetic amines.

Hypokalaemia and Hyperglycaemia

Beta-adrenergic agonist medicines may produce significant hypokalaemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient

hyperglycaemia in some patients. In clinical trials evaluating fluticasone furoate/vilanterol in subjects with asthma or COPD, there was no evidence of a treatment effect on serum glucose or potassium.

Effects on Fertility:

There are no fertility data in humans. Studies in rats showed no effect of vilanterol or fluticasone furoate on male or female fertility.

Use in Pregnancy (Category B3):

There are no adequate and well-controlled trials with fluticasone furoate/vilanterol in pregnant women. Corticosteroids and beta$_2$-agonists have been shown to be teratogenic in laboratory animals when administered systematically at relatively low dosage levels.

Maternal and fetal toxicity (likely due to the fluticasone furoate component) were observed in rat embryofetal development study with the fluticasone/vilanterol combination at fluticasone furoate doses of 29.5 and 82 µg/kg/day, respectively (equivalent to 3 and 9 times, respectively, the clinical exposure based on AUC).

In rabbits, there was evidence of maternal toxicity and embryotoxicity following inhalation exposure to vilanterol triphenylacetate at 591 and 62.7 µg/kg/day, respectively (equivalent to 150 and 14 times the clinical exposure based on AUC). A non-dose related increase in malformations, including the rare open eyelid, was also observed. In a separate study with subcutaneous exposure, increased incidence of open eye and increase in skeletal variations (indicative of developmental delay) occurred at 300 µg/kg/day (equivalent to 1000 times the clinical exposure based on AUC) with a NOAEL of 30 µg/kg/day (equivalent to 84 times the clinical exposure based on AUC).

Administration of Breo Ellipta to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

Use in Lactation:

There is limited information on the excretion of fluticasone furoate or vilanterol or their metabolites in human milk. However, other corticosteroids and beta$_2$-agonists are detected in human milk. A risk to breastfed newborns/infants cannot be excluded.

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

Paediatric Use:

Breo Ellipta should not be used in children (i.e. patients younger than 12 years of age).

Use in the Elderly:

Due to limited data in patients with asthma aged 75 years and older, Breo 200/25 is not recommended.

Genotoxicity:

Fluticasone furoate was not genotoxic in a standard battery of studies.

Vilanterol was negative in a complete battery of *in vitro* (Ames, UDS, SHE cell) assays and *in vivo* (rat bone marrow micronucleus) assays and equivocal in the mouse lymphoma assay. The weight of evidence suggests that vilanterol does not pose a genotoxic risk.

Carcinogenicity:

No carcinogenicity studies were performed with the fluticasone furoate/vilanterol triphenylacetate combination.

Fluticasone furoate 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.

Proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland were observed in lifetime inhalation studies with vilanterol, consistent with findings for other beta$_2$-agonists. There was no increase in tumour incidence in rats or mice at exposures 1- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Effect on Laboratory Tests:

Interactions with laboratory tests have not been established.

Ability to perform tasks that require Judgement, Motor or Cognitive Skills

There have been no studies to investigate the effect of fluticasone furoate/vilanterol on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology of fluticasone furoate or vilanterol.

INTERACTIONS WITH OTHER MEDICINES

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

Interaction with beta-blockers

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

Interaction with CYP3A4 inhibitors

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

Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there will be increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see Pharmacokinetics).

Interaction with P-glycoprotein inhibitors

Fluticasone furoate and vilanterol are both substrates of P-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.

Interaction with sympathomimetic medicinal products

Concomitant administration of other sympathomimetic agents (alone or as part of combination therapy) may potentiate the undesirable effects of Breo Ellipta. Breo Ellipta should not be used in conjunction with other long-acting $beta_2$-adrenergic agonists or medicinal products containing long-acting $beta_2$-adrenergic agonists.

Interaction with monoamine oxidase inhibitors and tricyclic antidepressants

Vilanterol, like other $beta_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

ADVERSE EFFECTS

Clinical trial data

The most frequent adverse events, based on studies including a comparator, are presented in Table 3 and Table 4 for asthma and COPD, respectively.

Table 3 Adverse Events With ≥3% Incidence With Fluticasone Furoate/Vilanterol in Asthma (Integrated Asthma Clinical Studies)

	Number (%) of Subjects						
Adverse Event (Preferred Term)	Placebo N=680	FF/VI 100/25 N=1467	FF/VI 200/25 N=455	FF 100 N=1544	FF 200 N=489	Placebo +ICS N=218	VI 25 +ICS N=216
Any AE	184 (27)	857 (58)	247 (54)	842 (55)	181 (37)	84 (39)	78 (36)
Headache	44 (6)	252 (17)	55 (12)	216 (14)	29 (6)	13 (6)	17 (8)
Nasopharyngitis	35 (5)	202 (14)	45 (10)	167 (11)	38 (8)	16 (7)	9 (4)
URTI[1]	10 (1)	110 (7)	32 (7)	109 (7)	8 (2)	10 (5)	4 (2)
Bronchitis	13 (2)	67 (5)	16 (4)	84 (5)	7 (1)	0	0
Oropharyngeal pain	7 (1)	53 (4)	16 (4)	68 (4)	14 (3)	8 (4)	7 (3)
Cough	8 (1)	64 (4)	14 (3)	68 (4)	10 (2)	1 (<1)	0
Sinusitis	5 (<1)	54 (4)	7 (2)	45 (3)	10 (2)	3 (1)	0
Back pain	2 (<1)	51 (3)	17 (4)	48 (3)	7 (1)	1 (<1)	2 (<1)
Influenza	1 (<1)	51 (3)	8 (2)	40 (3)	9 (2)	3 (1)	1 (<1)
Pharyngitis	8 (1)	37 (3)	8 (2)	48 (3)	4 (<1)	3 (1)	2 (<1)
Dysphonia	4 (<1)	38 (3)	13 (3)	21 (1)	8 (2)	4 (2)	0
Rhinitis allergic	5 (<1)	49 (3)	5 (1)	27 (2)	1 (<1)	1 (<1)	4 (2)
Abdominal pain upper	3 (<1)	44 (3)	12 (3)	28 (2)	2 (<1)	3 (1)	2 (<1)
Pyrexia	1 (<1)	33 (2)	16 (4)	22 (1)	5 (1)	1 (<1)	5 (2)
Oral candidiasis	0	24 (2)	15 (3)	17 (1)	5 (1)	0	0
Extrasystoles	0	5 (<1)	15 (3)	0	0	0	0

Note: The integrated asthma data set is based on 11 Phase II and III studies and a total of 7,034 patients.
URTI = Upper respiratory tract infection

Table 4 Adverse Events With ≥3% Incidence With Fluticasone Furoate/Vilanterol in COPD (Studies HZC112206/HZC112207)

	Placebo N=412	FF/VI 100/25 N=410	FF/VI 200/25 N=205	VI 25 N=408	FF 100 N=410	FF 200 N=203
Preferred Term, n (%)						
Nasopharyngitis	31 (8)	35 (9)	13 (6)	41 (10)	32 (8)	20 (10)
Headache	20 (5)	29 (7)	15 (7)	36 (9)	30 (7)	11 (5)
Upper respiratory tract infection	13 (3)	29 (7)	7 (3)	20 (5)	16 (4)	5 (2)
Oral/ Oropharyngeal candidiasis*	9 (2)	22 (5)	9 (4)	9 (2)	13 (3)	13 (6)

Note: AEs reported by 3% or more of subjects in any treatment group and at a higher incidence (≥1%) than placebo
*Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis fungal.

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

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

These adverse reactions are listed by system organ class and frequency. The following convention has been used for the classification of adverse reactions:

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1000 to <1/100.

Rare ≥1/10000 to <1/1000

Very rare <1/10000

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

Description of selected adverse reactions

<u>*Pneumonia</u>

In two replicate 12 month studies in a total of 3,255 patients with COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the fluticasone furoate (at strengths of 50, 100, and 200 micrograms)/vilanterol 25 micrograms combination than in those receiving vilanterol 25 micrograms alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving fluticasone furoate/vilanterol (all strengths) and in <1% of patients receiving vilanterol. In these studies, nine fatal cases of pneumonia were reported. Of these, seven were reported during treatment with fluticasone furoate/vilanterol 200/25 micrograms, one during treatment with fluticasone furoate/vilanterol 100/25 micrograms and one post-treatment with vilanterol monotherapy. Risk factors for pneumonia observed in these studies included current smokers, patients with a history of prior pneumonia, patients with a body mass index <25 kg/m^2 and patients with an FEV_1<50% predicted (see Precautions).

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with fluticasone furoate/vilanterol 100/25 microgram strength (9.6/1000 patient years) was similar to placebo (8.0/1000 patient years). There was a higher incidence of pneumonia in the 200/25 microgram strength (18.4/1000 patient years) compared to the 100/25 microgram strength. Few of the pneumonia events led to hospitalisation with either strength, and there were no observed differences in the incidence of serious events between the two treatment strengths.

**Fractures

In two replicate 12 month studies in a total of 3,255 patients with COPD the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all fluticasone furoate/vilanterol groups (2%) compared with the vilanterol 25 micrograms group (<1%). Although there were more fractures in the fluticasone furoate/vilanterol groups compared with the vilanterol 25 micrograms group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the fluticasone furoate/vilanterol and vilanterol treatment arms.

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of fractures was <1%, and usually associated with trauma.

Post-marketing data

There are limited post-marketing data available. Because of the limited long-term safety data (beyond one year) for Breo Ellipta, assumptions about long-term safety for this combination product have been based on data from pharmaceuticals in the same class.

DOSAGE AND ADMINISTRATION

Breo Ellipta is for inhalation only.

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

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

Asthma

Patients should be made aware that Breo Ellipta must be used regularly, even when asymptomatic.

If symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist should be taken for immediate relief.

Patients should be regularly reassessed by a healthcare professional so that the strength of Breo Ellipta they are receiving remains optimal and is only changed on medical advice. To minimise adverse reactions, inhaled corticosteroids should be used at the lowest dose that maintains symptom control.

Adults and adolescents aged 12 years and over

The recommended dose of Breo Ellipta is:

One inhalation of Breo Ellipta 100/25 micrograms once daily

or

One inhalation of Breo Ellipta 200/25 micrograms once daily

A starting dose of Breo Ellipta 100/25 micrograms should be considered for patients who require a mid dose of inhaled corticosteroid in combination with a long acting $beta_2$-agonist.

Breo Ellipta 200/25 micrograms should be considered for patients who require a higher dose of inhaled corticosteroid in combination with a long acting $beta_2$-agonist.

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

Table 5 Recommended Doses of Breo Ellipta for asthma patients on existing therapies

Existing therapy	Recommended Dose
For patients uncontrolled on FP 100 micrograms to FP250 micrograms twice daily or equivalent (200-400 micrograms twice daily of budesonide) For patients uncontrolled on low doses of LABA/ICS combinations (FP/salmeterol 100/50 micrograms twice daily or Budesonide/eformoterol 200/6 micrograms one or two actuations twice daily) For patients controlled on mid doses of LABA/ICS (FP/salmeterol 250/50 micrograms twice daily or budesonide/eformoterol 200/6 micrograms two actuations twice daily)	Breo Ellipta 100/25 micrograms once daily
For patients uncontrolled on FP 500 micrograms twice daily or equivalent (600-800 micrograms twice daily of budesonide) For patients uncontrolled on mid doses of LABA/ICS combinations (FP/salmeterol 250/50 micrograms twice daily or budesonide/eformoterol 200/6 micrograms two actuations twice daily) For patients controlled on high dose LABA/ICS combinations (FP/salmeterol 500/50 micrograms twice daily or budesonide/eformoterol 400/12 micrograms two actuations twice daily)	Breo Ellipta 200/25 micrograms once daily

Prescribers should be aware that 100 micrograms of fluticasone furoate is a medium dose of inhaled corticosteroid and 200 micrograms of fluticasone furoate is a high dose of inhaled corticosteroid. In patients with asthma, 100 micrograms of fluticasone furoate taken once daily produces similar effects to fluticasone propionate 250 micrograms taken twice daily and 200 micrograms of fluticasone furoate taken once daily produces similar effects to fluticasone propionate 500 micrograms taken twice daily.

To minimise adverse reactions, inhaled corticosteroids should be used at the lowest dose that maintains symptom control. Patients should be assessed at regular intervals. In patients whose asthma is well controlled and stable the Breo Ellipta dose may carefully be down-titrated to the lowest strength of Breo Ellipta.

The next step should consider the cessation of Breo Ellipta and transfer to an appropriate inhaled corticosteroid containing regimen. When deemed clinically appropriate the inhaled corticosteroid dose should be further adjusted to the lowest dose at which effective control of asthma is maintained.

Additional recommendations for adolescents aged 12 years and older

Down-titration to the lowest inhaled corticosteroid dose is especially important in adolescents who may be more susceptible to systemic corticosteroid effects (see Precautions). When down-titrating to another product, consideration should be given to maintaining a once-daily regimen to facilitate compliance.

Children aged less than 12 years

Breo Ellipta should not be used in children younger than 12 years of age.

COPD

Adults

The recommended dose of Breo Ellipta is:

One inhalation of Breo Ellipta 100/25 micrograms once daily.

Breo Ellipta 200/25 micrograms is not indicated for patients with COPD. There is a potential increased risk of pneumonia and corticosteroid-related adverse reactions with the 200/25 microgram dose (see Precautions and Adverse Effects).

Asthma and COPD

Elderly

Due to limited data in patients with asthma aged 75 years and older, Breo 200/25 is not recommended.

Renal impairment

No dose adjustment is required for patients with renal impairment (see Special Patient Populations – Renal Impairment).

Hepatic Impairment

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

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

For patients with moderate or severe hepatic impairment the maximum dose is 100/25 micrograms (see Pharmacokinetics).

OVERDOSAGE

Symptoms and signs

There are no data available from clinical trials on overdose with Breo Ellipta.

An overdose of Breo Ellipta may produce signs and symptoms due to the individual components' actions, including those seen with overdose of other beta$_2$-agonists and consistent with the known inhaled corticosteroid class effects (see Precautions).

Treatment

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

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

Further management should be as clinically indicated. For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Storage

Store below 30^{o}C.

Following removal from the tray, the product may be stored for a maximum period of 1 month.

Nature and Contents of Container

Moulded plastic device containing two double foil blister strips. Each foil strip contains 14 or 30 regularly distributed blisters with one strip containing a powder formulation of 100 micrograms of fluticasone furoate and the other strip containing 25 micrograms of vilanterol (as trifenatate). Each delivered dose (the dose leaving the mouthpiece) contains of 92 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate).

Moulded plastic device containing two double foil blister strips. Each foil strip contains 14 or 30 regularly distributed blisters with one strip containing a powder formulation of 200

micrograms of fluticasone furoate and the other strip containing 25 micrograms of vilanterol (as trifenatate). Each delivered dose (the dose leaving the mouthpiece) contains of 184 micrograms of fluticasone furoate and 22 micrograms of vilanterol (as trifenatate).

Not all pack sizes may be distributed in Australia.

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd,
Level 4,
436 Johnston Street,
Abbotsford, Victoria, 3067

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

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 -don't eat or inhale it.

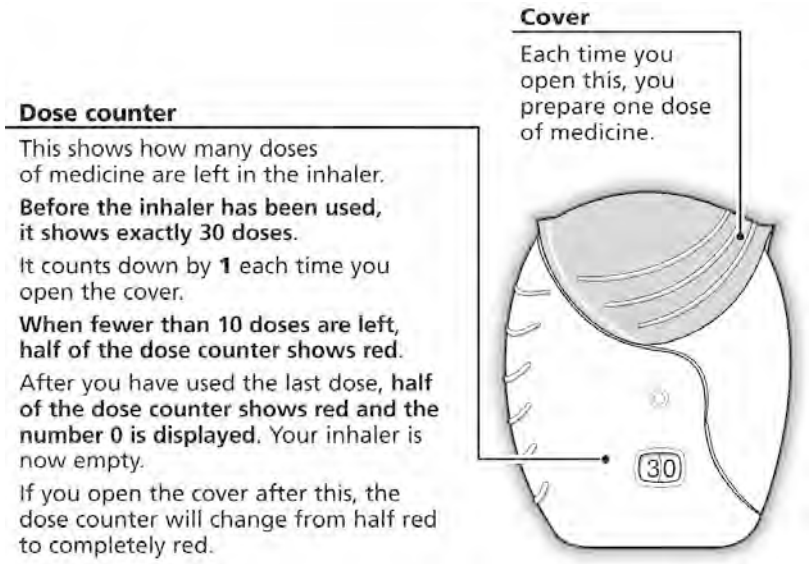
When you take the inhaler out of its box, it will be in the 'closed' position. **Don't open it until you are ready to inhale a dose of medicine.**

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

Step 1: Read this before you start

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

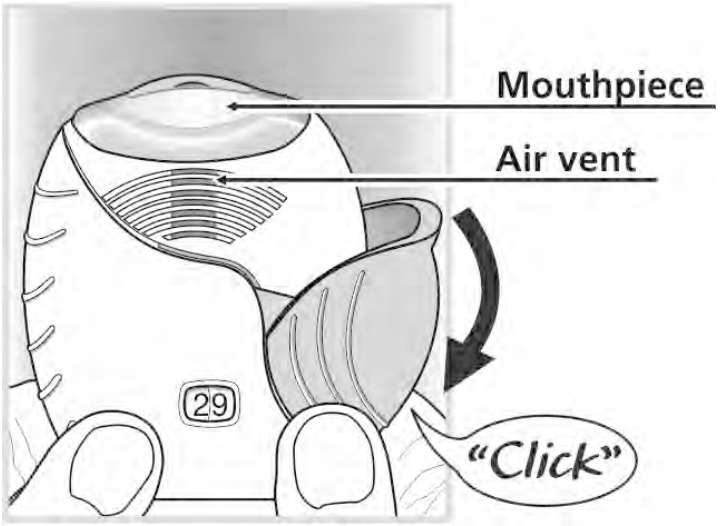
The lost dose will be securely held inside the inhaler, but it will no longer be available. It is not possible to accidentally take extra medicine or a double dose in one inhalation.



Step 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.

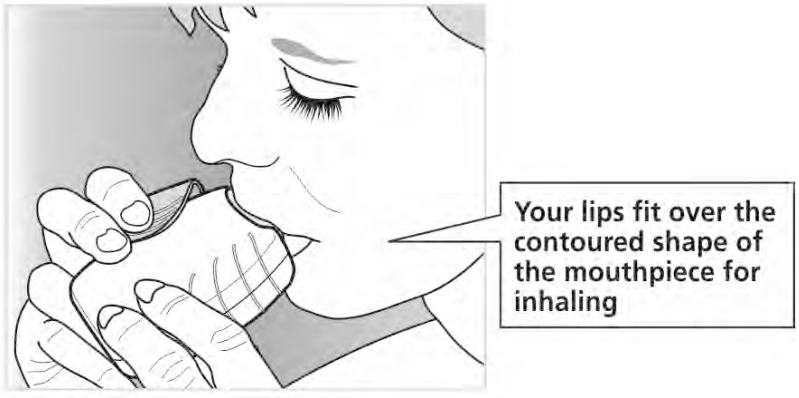
The dose counter counts down by **1** to confirm.

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

! **Do not shake the inhaler at any time.**

Step 3: Inhale your medicine

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



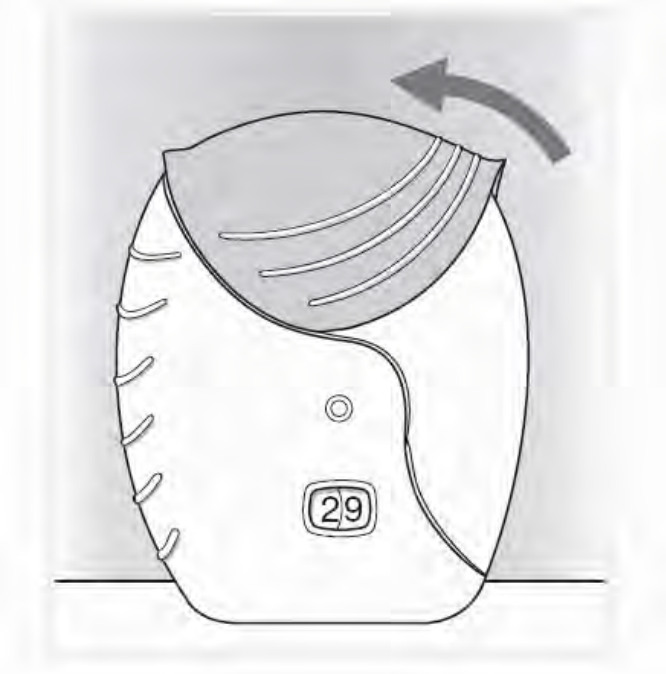
- Take one long, steady, deep breath in. Hold this breath for as long as possible (about 3-4 seconds).
- Remove the inhaler from your mouth.
- Breathe out slowly and gently.

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

Step 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.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
17 April 2014

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Version 1.0