

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BREO ELLIPTA fluticasone furoate (100 micrograms or 200 micrograms)/vilanterol (as trifenate) (25 micrograms), powder for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BREO ELLIPTA 100 micrograms/25 micrograms: 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).

BREO ELLIPTA 200 micrograms/25 micrograms: 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 - List of excipients.

3. PHARMACEUTICAL FORM

Powder for inhalation.

White powder in a light grey inhaler (Ellipta) with a pale blue mouthpiece cover and a dose counter.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Asthma

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

Chronic Obstructive Pulmonary Disease (COPD)

BREO ELLIPTA is indicated for symptomatic treatment of adult patients with COPD with a FEV₁ < 70% predicted normal (post-bronchodilator) in patients with an exacerbation history.

4.2. Dosage and method of administration

Dose

Asthma

Adults and adolescents aged 12 years and over

One inhalation of BREO ELLIPTA 100/25 micrograms once daily

or

One inhalation of BREO ELLIPTA 200/25 micrograms once daily

Patients usually experience an improvement in lung function within 15 minutes of inhaling BREO 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 BREO ELLIPTA 100 micrograms/25 micrograms should be considered for adults and adolescents 12 years and over who require a low to mid-dose of inhaled corticosteroid (ICS) in combination with a long-acting beta₂-agonist (LABA). If patients are inadequately controlled on BREO ELLIPTA 100 micrograms/25 micrograms, consider increasing the dose to 200 micrograms/25 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.

BREO ELLIPTA 200 micrograms/25 micrograms should be considered for adults and adolescents 12 years and over who require a higher dose of ICS in combination with a LABA.

The maximum recommended dose is BREO ELLIPTA 200 micrograms/25 micrograms once daily.

Prescribers should be aware that in patients with asthma, 100 micrograms of fluticasone furoate taken once daily produces similar effects to fluticasone propionate 250 micrograms taken twice daily.

Children aged under 12 years:

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

COPD

Adults aged 18 years and over

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

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

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

Children

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

Special Populations

Elderly

No dosage adjustment is required in patients over 65 years (see Section 5.2 – Pharmacokinetic properties, Special Patient Populations).

Renal impairment

No dose adjustment is required for patients with renal impairment (see Section 5.2 – Pharmacokinetic properties, Special Patient Populations).

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 (area under the curve [AUC]) (see Section 5.2 - Pharmacokinetic properties).

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 one inhalation of BREO ELLIPTA 100/25 micrograms once daily.

Paediatric population

The safety and efficacy of BREO ELLIPTA for the treatment of asthma has not been established in children less than 12 years of age. No data are available.

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

Method of administration

BREO ELLIPTA is for (oral) inhalation only.

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

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

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

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

For instructions on the use and handling of this medicine, please refer to Section 6.6 - Special precautions for disposal and other handling.

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Exacerbations

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

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

Paradoxical bronchospasm

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. 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 BREO ELLIPTA. In a placebo-controlled study in subjects with a history of, or an increased risk of cardiovascular disease, there was no increase in the risk of cardiovascular events, serious cardiovascular events, or adjudicated cardiovascular deaths in patients receiving fluticasone furoate/vilanterol compared with placebo (see Section 4.8 - Undesirable effects). However, 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 Section 5.2 – Special Patient Populations).

Systemic corticosteroid effects

Systemic effects may occur with any ICS, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include hypothalamic-pituitary-adrenal (HPA) axis suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract, glaucoma, central serous chorioretinopathy (CSCR) and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

As with all medication containing corticosteroids, BREO ELLIPTA should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections.

Hyperglycaemia

There have been reports of increases in blood glucose levels with fluticasone furoate/vilanterol. This should be considered in patients with a history of, or with risk factors for, diabetes mellitus (see Section 4.8 - Undesirable effects).

Pneumonia

An increase in pneumonia has been observed in patients with COPD receiving BREO ELLIPTA. There was also an increased incidence of pneumonias resulting in hospitalisation. In some incidences, these pneumonia events were fatal (see Section 5.1 – Pharmacodynamic properties, Clinical efficacy and safety, and Section 4.8 - Undesirable 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 BREO ELLIPTA include current smokers, patients with a history of prior pneumonia, patients with a body mass index < 25 kg/m² and patients with a (forced expiratory volume) FEV₁ < 50% predicted. These factors should be considered when BREO ELLIPTA is prescribed and treatment should be re-evaluated if pneumonia occurs.

Patients with asthma taking BREO ELLIPTA 200/25 micrograms may be at an increased risk of pneumonia compared with those receiving BREO ELLIPTA 100/25 or placebo (see Section 4.8 - Undesirable effects). No risk factors were identified.

4.5. Interaction with other medicines and other forms of interaction

Interaction studies have only been conducted in adults. Clinically significant drug interactions mediated by fluticasone furoate or vilanterol at clinical doses are considered unlikely due to the low plasma concentrations achieved after inhaled dosing.

Interaction with beta-blockers

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

Interaction with CYP3A4 inhibitors

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

Care is advised when co-administering with strong CYP 3A4 inhibitors (e.g. ketoconazole, ritonavir) as there is potential for an increased systemic exposure to both fluticasone furoate and vilanterol, which could lead to an increase in the potential for adverse reactions (see Section 5.2 - Pharmacokinetic properties).

Interaction with P-glycoprotein inhibitors

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

4.6. Fertility, pregnancy and lactation

Pregnancy

There has been limited pregnancy exposure in humans.

Animal studies have shown reproductive toxicity after administration of beta₂-agonists and corticosteroids (see Section 5.3 - Preclinical safety data).

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.

Breast-feeding

There is limited information on the excretion of fluticasone furoate or vilanterol or their metabolites in human milk. However, other corticosteroids and beta₂-agonists are detected in human milk (see Section 5.3 - Preclinical safety data). 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.

Fertility

There are no fertility data in humans. Animal studies showed no effect of vilanterol or fluticasone furoate on fertility (see Section 5.3 - Preclinical safety data).

4.7. Effects on ability to drive and use machines

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

4.8. 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 BREO ELLIPTA. In the asthma clinical development program, a total of 7,034 patients were included in an integrated assessment of adverse reactions. In the COPD clinical development program, a total of 6,237 subjects were included in an integrated assessment of adverse reactions.

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

Tabulated list of adverse reactions

Adverse reactions noted in clinical trials are listed in the table below by system organ class and frequency. The following convention has been used for the classification of adverse reactions:

Very common: $\geq 1/10$
Common: $\geq 1/100$ to $< 1/10$
Uncommon: $\geq 1/1000$ to $< 1/100$
Rare: $\geq 1/10000$ to $< 1/1000$
Very rare: $< 1/10000$

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
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

System organ class	Adverse reaction(s)	Frequency
Musculoskeletal and connective tissue disorders	Arthralgia, Back pain Fractures***	Common
General disorders and administration site conditions	Pyrexia	Common

Description of selected adverse reactions

**Pneumonia (see Section 4.4 – Special warnings and precautions for use)*

In two replicate, 12-month studies in a total of 3,255 patients with COPD (mean post-bronchodilator screening FEV₁ 45% of predicted, standard deviation [SD] 13%) who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia (6%-7%) reported in patients receiving the fluticasone furoate (at strengths of 50, 100, and 200 micrograms)/vilanterol 25 micrograms combination than in those receiving vilanterol 25 micrograms alone (3%). Pneumonia which required hospitalisation occurred in 3% of patients receiving BREO ELLIPTA (all strengths) and in < 1% of patients receiving vilanterol. In these studies, nine fatal cases of pneumonia were reported. Of these, seven were reported during treatment with BREO ELLIPTA 200/25 micrograms, one during treatment with BREO ELLIPTA 100/25 micrograms and one post-treatment with vilanterol monotherapy.

In SUMMIT, a multi-centre, randomised study (HZC113782), 16,568 subjects received fluticasone furoate/vilanterol 100/25 micrograms, fluticasone furoate 100 micrograms, vilanterol 25 micrograms, or placebo for a mean of 1.7 years. Subjects had moderate COPD (mean post-bronchodilator screening FEV₁ 60% of predicted, SD 6%) and a history of, or an increased risk of, cardiovascular disease. The adverse events of pneumonia are noted in the table below.

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 100/25 N=4,140	FF 100 N=4,157	VI 25 N=4,140	Placebo N=4,131
Pneumonia	237 (6) [39.5]	228 (5) [42.4]	163 (4) [27.7]	214 (5) [38.4]
Serious pneumonia	140 (3) [22.4]	146 (4) [25.1]	104 (3) [16.4]	127 (3) [22.2]
Adjudicated pneumonia deaths	13 (<1) [1.8]	10 (<1) [1.5]	6 (<1) [0.9]	9 (<1) [1.4]

In an integrated analysis of 11 studies in asthma (7,034 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with BREO ELLIPTA 100/25 microgram strength (9.6/1000 patient years) was similar to placebo (8.0/1000 patient years). There was a higher incidence of pneumonia in the 200/25 microgram strength (18.4/1000 patient years) compared to the 100/25 microgram strength. Few of the pneumonia events led to hospitalisation with either

strength, and there were no observed differences in the incidence of serious events between the two treatment strengths.

****Cardiovascular events (see Section 4.4 – Special warnings and precautions for use)**

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

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 100/25 N=4,140	FF 100 N=4,157	VI 25 N=4,140	Placebo N=4,131
Cardiovascular	735 (18) [163]	699 (17) [157]	707 (17) [157]	695 (17) [164]
Serious cardiovascular	350 (8) [64.5]	320 (8) [58.1]	337 (8) [59.2]	318 (8) [63.2]
Adjudicated cardiovascular deaths	82 (2) [11.7]	80 (2) [11.6]	90 (2) [12.9]	86 (2) [13.0]

*****Fractures**

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

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

On-treatment Events	Number (%) of Subjects [Event Rate Per 1000 Treatment Years]			
	FF/VI 100/25 N=4,140	FF 100 N=4,157	VI 25 N=4,140	Placebo N=4,131
All fractures	82 (2) [13.6]	66 (2) [12.8]	74 (2) [13.2]	69 (2) [11.5]
Fractures commonly associated with ICS use	23 (<1) [3.4]	24 (<1) [3.9]	17 (<1) [2.4]	13 (<1) [2.1]

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

Post-Marketing Experience

System organ class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria	Rare
Metabolism and	Hyperglycaemia	Uncommon

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: <https://nzphvc.otago.ac.nz/reporting/>.

4.9. Overdose

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 beta₂-agonists and consistent with the known ICS class effects (see Section 4.4 – Special warnings and precautions for use).

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.

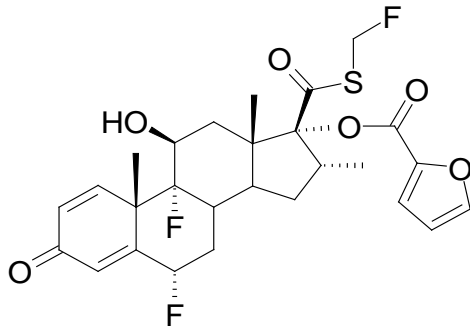
Further management should be as clinically indicated or as recommended by the national poisons centre, where available. For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

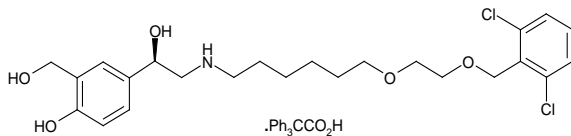
5.1. Pharmacodynamic properties

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

Chemical structure of fluticasone furoate



Chemical structure of vilanterol trifenate



Mechanism of action

Fluticasone furoate and vilanterol represent two classes of medications (a synthetic corticosteroid and a selective LABA).

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 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 catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of

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

Molecular interactions occur between corticosteroids and LABAs, whereby steroids activate the beta₂-receptor gene, increasing receptor number and sensitivity; and LABAs prime the glucocorticoid receptor for steroid-dependent activation and enhance cell nuclear translocation. These synergistic interactions are reflected in enhanced anti-inflammatory activity, which has been demonstrated *in vitro* and *in vivo* in a range of inflammatory cells relevant to the pathophysiology of both asthma and COPD. In peripheral blood mononuclear cells from subjects with COPD, a larger anti-inflammatory effect was seen in the presence of the combination of fluticasone furoate/vilanterol compared with fluticasone furoate alone at concentrations achieved with clinical doses.

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 BREO ELLIPTA in adult and adolescent patients with persistent asthma. All subjects were using an ICS 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 BREO ELLIPTA 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 BREO ELLIPTA 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) 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 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	193 mL	210 mL	36 mL	172 mL
P value (95% CI)	p < 0.001 (108, 277)	p < 0.001 (127, 294)	p=0.405 (-48, 120)	p < 0.001 (87, 258)
Weighted Mean Serial FEV ₁ over 0-24 hours post-dose				
Treatment difference	136 mL	206 mL	116 mL	302 mL

Study No.	HZA106829		HZA106827	
P value (95% CI)	p=0.048 (1, 270)	p=0.003 (73, 339)	p=0.06 (-5, 236)	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)	33.5 L/min p < 0.001 (25.3, 41.7)	32.9 L/min p < 0.001 (24.8, 41.1)	14.6 L/min p < 0.001 (7.9, 21.3)	33.3 L/min p < 0.001 (26.5, 40.0)
Change from Baseline in PM Peak Expiratory Flow				
Treatment difference P value (95% CI)	30.7 L/min p < 0.001 (22.5, 38.9)	26.2 L/min p < 0.001 (18.0, 34.3)	12.3 L/min P < 0.001 (5.8, 18.8)	28.2 L/min p < 0.001 (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 BREO ELLIPTA 100 micrograms/25 micrograms [n=1009] or FF 100 micrograms [n=1010] both administered once daily. The primary endpoint was the time to first severe asthma exacerbation. A severe asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalisation 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 BREO ELLIPTA 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 BREO ELLIPTA 100 micrograms/25 micrograms group (approximately 1 in every 7 years). The ratio of the exacerbation rate for BREO ELLIPTA 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 BREO ELLIPTA 100 micrograms/25 micrograms compared with FF 100 (p=0.014). The 24-hour bronchodilator effect of BREO ELLIPTA was maintained throughout a one-year treatment period with no evidence of loss in efficacy (no tachyphylaxis). BREO ELLIPTA 100 micrograms/25 micrograms consistently demonstrated 83 mL to 95 mL improvements in trough FEV₁ at Weeks 12, 36 and 52 and Endpoint compared with FF 100 micrograms (p<0.001 95% CI 52, 126mL at Endpoint). Forty-four percent of patients in the BREO ELLIPTA 100 micrograms/25 micrograms 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

In a 24-week study (HZA113091) in adult and adolescent patients with persistent asthma, both BREQ ELLIPTA 100 micrograms/25 micrograms given once daily in the evening and salmeterol/FP 50/250 micrograms given twice daily demonstrated improvements from baseline in lung function. Adjusted mean treatment increases from baseline in weighted mean 0-24 hours FEV₁ of 341 mL (BREQ ELLIPTA) 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).

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) 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 100 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 BREQ ELLIPTA 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 randomised to receive BREQ ELLIPTA 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 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 BREQ ELLIPTA 100 micrograms/25 micrograms compared with FF 100 micrograms or vilanterol 25 micrograms alone. Both BREQ ELLIPTA (100 micrograms/25 micrograms) and FF 100 micrograms virtually abolished the late asthmatic response compared with vilanterol alone. BREQ ELLIPTA 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.

Bronchoprotective and HPA-axis effects study

The bronchoprotective and HPA-axis effects of FF versus FP or budesonide (BUD) were evaluated in an escalating repeat-dose, placebo-controlled, crossover study (203162) in 54 adults with a history of asthma, characterised by airway hyperresponsiveness and FEV₁ ≥65% predicted. Patients were randomised to one or two treatment periods,

comprising five 7-day dose-escalation phases of FF (25, 100, 200, 400, 800 micrograms/day), FP (50, 200, 500, 1,000, 2,000 micrograms/day), BUD (100, 400, 800, 1,600, 3,200 micrograms/day), or placebo. After each dose-escalation phase, bronchoprotection via airway hyperresponsiveness to adenosine-5'-monophosphate (AMP) challenge (provocative concentration causing $\geq 20\%$ decline in FEV₁ [AMP PC₂₀]) and 24-hour weighted mean plasma cortisol were assessed.

Overall, and within approved dose ranges for asthma, FF (100 to 200 micrograms/day) provided more protection against airway hyperresponsiveness (higher AMP PC₂₀) with less systemic activity (less cortisol suppression) than FP or BUD. Bronchoprotection (AMP PC₂₀, mg/mL) and HPA-axis effects (cortisol suppression, %) across the therapeutic dose ranges were 81 to 116 mg/mL and 7 to 14% for FF (100 to 200 micrograms/day), 20 to 76 mg/mL and 7 to 50% for FP (200 to 2,000 micrograms/day), and 24 to 54 mg/mL and 13 to 44% for BUD (400 to 1,600 micrograms/day), respectively. The therapeutic index (dose for 50% cortisol suppression/dose for 50% maximum bronchoprotection) was higher for FF (18.55) compared with FP (1.84) or BUD (1.31).

Chronic Obstructive Pulmonary Disease

The COPD clinical development programme included a 12-week (HZC113107), two 6-month (HZC112206, HZC112207), two one-year randomised controlled studies (HZC102970, HZC102871), and one long-term study (SUMMIT) in patients with a clinical diagnosis of COPD. 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 BREO ELLIPTA 50 micrograms/25 micrograms [n=206] and BREO ELLIPTA 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 BREO ELLIPTA 100 micrograms/25 micrograms [n=204] and BREO ELLIPTA 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 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) dyspnoea score ≥ 2 (scale 0-4) at the 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, BREO ELLIPTA 100 micrograms/25 micrograms showed clinically meaningful improvements in lung function. At Day 169, BREO ELLIPTA 100 micrograms/25 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, 121 mL, p < 0.001), respectively, compared to placebo. BREO ELLIPTA 100 micrograms/25 micrograms

increased trough FEV₁ by 46 mL compared to vilanterol (95% CI: 8, 83 mL, p=0.017). At Day 168, BREO ELLIPTA 100 micrograms/25 micrograms and vilanterol increased adjusted mean weighted mean FEV₁ over 0-4 hours by 193 mL (95% CI: 156, 230 mL, p < 0.001) and 145 mL (95% CI: 108, 181 mL, p < 0.001) respectively compared to placebo. BREO ELLIPTA 100/25 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).

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 BREO ELLIPTA 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 BREO ELLIPTA 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 BREO ELLIPTA 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 BREO ELLIPTA 200 micrograms/25 micrograms, BREO ELLIPTA 100 micrograms/25 micrograms, BREO ELLIPTA 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 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 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 (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 BREO ELLIPTA 100 micrograms/25 micrograms once daily resulted in a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol (p ≤ 0.024). Reductions in risk of time to first moderate or severe exacerbation and rate of exacerbations requiring

corticosteroid use were also observed with fluticasone furoate/vilanterol 100/25 micrograms once daily compared with vilanterol.

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

Endpoint	HZC102970		HZC102871		HZC102970 and HZC102871 integrated	
	Vilanterol (n=409)	Breo Ellipta 100/25 (n=403)	Vilanterol (n=409)	Breo Ellipta 100/25 (n=403)	Vilanterol (n=818)	Breo Ellipta 100/25 (n=806)
Moderate and severe exacerbations						
Adjusted mean annual rate	1.14	0.90	1.05	0.70	1.11	0.81
Ratio vs VI		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)
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		< 0.001
Exacerbations requiring systemic/oral corticosteroids						
Annual rate	0.86	0.66	0.84	0.52	0.87	0.61
Ratio vs VI		0.77		0.62		0.70
95% CI		(0.60,0.99)		(0.49, 0.78)		(0.59, 0.83)
p-value		0.041		< 0.001		< 0.001
% reduction		23		38		30
95% CI		(1, 40)		(22, 51)		(17, 41)

In an integrated analysis of HZC102970 and HZC102871 at Week 52, an improvement was seen when comparing the BREO ELLIPTA 100 micrograms/25 micrograms vs. vilanterol 25 micrograms in adjusted mean trough FEV₁ (42 mL 95% CI: 19, 64 mL, p < 0.001). The 24-hour bronchodilator effect of BREO ELLIPTA 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, BREO ELLIPTA

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 BEO ELLIPTA 100 micrograms/25 micrograms vs. vilanterol 25 micrograms in adjusted mean trough FEV₁ (44 mL 95% CI: 15, 73 mL, $p=0.003$).

Long-term study

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

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

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

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

Fluticasone furoate/vilanterol demonstrated a larger mean change from baseline in post-bronchodilator FEV₁ at Day 360 compared with placebo (89 mL; 95% CI: 76, 102; $p < 0.001$), FF (40 mL; 95% CI: 27, 53; $p < 0.001$), and VI (26 mL; 95% CI: 13, 39; $p < 0.001$). The adjusted mean change from baseline was: fluticasone furoate/vilanterol 50 mL, placebo, -39 mL; fluticasone furoate, 9 mL; vilanterol, 24 mL.

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

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

Studies versus salmeterol/fluticasone propionate combinations

In a 12-week study (HZC113107) in COPD patients both BREO ELLIPTA 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 FEV₁ of 130 mL (BREO ELLIPTA) 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, 63 mL) 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 BREO ELLIPTA 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)).

5.2. Pharmacokinetic properties

Absorption

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

Distribution

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

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

Fluticasone furoate and vilanterol are substrates for P-gp, however, concomitant administration of BREO ELLIPTA 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.

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

Elimination

Following oral administration fluticasone furoate was eliminated in humans mainly by metabolism with metabolites being excreted almost exclusively in faeces, with < 1% of the recovered radioactive dose eliminated in the urine. The apparent plasma elimination half-life of fluticasone furoate following inhaled administration of BREO ELLIPTA 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 BREO ELLIPTA was, on average, 2.5 hours.

Special Patient Populations

Children

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

The pharmacokinetics of BREO ELLIPTA in patients less than 12 years of age has not been studied. The safety and efficacy of BREO ELLIPTA in children under the age of 12 years has not yet been established.

Elderly

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

There was no evidence for age (12-84) to affect the PK of fluticasone furoate 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.

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

Renal impairment

A clinical pharmacology study of BREO ELLIPTA 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 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 BREO ELLIPTA 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 (BREO ELLIPTA 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 Section 4.2 - Dosage and method of administration).

Following repeat dosing of BREO ELLIPTA 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 BREO ELLIPTA 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.

For patients with moderate to severe hepatic impairment, the 100/25 micrograms dose should be used (see Section 4.2 - Dosage and method of administration).

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 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).

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.

Carcinogenesis/mutagenesis

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

Genetic toxicity studies indicate vilanterol does not represent a genotoxic hazard to humans. Consistent with findings for other beta₂-agonists, in lifetime inhalation studies vilanterol caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

Reproductive Toxicology

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate (which contains milk protein)
Magnesium stearate

6.2. Incompatibilities

None reported.

6.3. Shelf life

2 years

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

6.4. Special precautions for storage

Store below 30°C. If stored in the refrigerator, allow the inhaler to return to room temperature for at least an hour before use.

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

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

BREO ELLIPTA 100 micrograms/25 micrograms: Packs containing a single inhaler providing either 14 or 30 doses.

BREO ELLIPTA 200 micrograms/25 micrograms: Packs containing a single inhaler providing either 14 or 30 doses.

Not all pack sizes may be distributed in New Zealand.

6.6. Special precautions for disposal and other handling

Disposal

Any unused medicine or water material should be disposed of in accordance with local requirements.

Instructions for handling

The Ellipta inhaler is provided in a foil laminate tray containing a desiccant sachet. The tray provides moisture protection and should only be opened when you are ready to use it for the first time. Once opened the desiccant sachet should be discarded.

Only open the Ellipta inhaler cover when you are ready to take a dose.

If you open and close the cover of the Ellipta inhaler without inhaling the medicine, you will lose the dose. The dose will be securely held inside the inhaler, but it will be no longer available. It is not possible to accidentally take extra medicine or a double dose in one inhalation.

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.

Your device may contain either 30 or 14 starting doses.

Important

The dose-counter indicates the number of doses left. Patients should consider getting a replacement when the counter shows the number 05. When the counter shows a full solid red background it must be replaced.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
12 December 2013

10. DATE OF REVISION OF THE TEXT

17 September 2020

Summary table of changes:

Section changed	Summary of new information
5.1	Addition of information from Bronchoprotective and HPA-axis effects study (Clinical Study 203162)

Version 9.0

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