HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BREO ELLIPTA safely and effectively. See full prescribing information for BREO ELLIPTA.

BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder), for oral inhalation use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES ----------

Indications and Usage, Maintenance Treatment of Asthma (1.2)	05/2023
Dosage and Administration, Recommended Dosage for Maintenance Treatment of Asthma (2.3)	05/2023
Warnings and Precautions, Effect on Growth (5.14)	05/2023

---------- INDICATIONS AND USAGE----------

BREO ELLIPTA is a combination of fluticasone furoate, a corticosteroid, and vilanterol, a long-acting beta$_2$-adrenergic agonist (LABA), indicated for:

- the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). (1.1)
- the maintenance treatment of asthma in patients aged 5 years and older. (1.2)

Limitations of Use: Not indicated for relief of acute bronchospasm. (1.3, 5.2)

----------DOSAGE AND ADMINISTRATION ----------

- For oral inhalation only. (2.3)
- Maintenance treatment of COPD: 1 actuation of BREO ELLIPTA 100/25 mcg once daily administered by oral inhalation. (2.1)
- Maintenance treatment of asthma in adult patients aged 18 years and older: 1 actuation of BREO ELLIPTA 100/25 mcg or BREO ELLIPTA 200/25 mcg once daily administered by oral inhalation. (2.2)
- Maintenance treatment of asthma in pediatric patients aged 12 to 17 years: 1 actuation of BREO ELLIPTA 100/25 mcg once daily administered by oral inhalation. (2.2)
- Maintenance treatment of asthma in pediatric patients aged 5 to 11 years: 1 actuation of BREO ELLIPTA 50/25 mcg once daily administered by oral inhalation. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------

Inhalation powder:

- 50 mcg fluticasone furoate and 25 mcg vilanterol (50/25 mcg) per actuation (3)
- 100 mcg fluticasone furoate and 25 mcg vilanterol (100/25 mcg) per actuation (3)
- 200 mcg fluticasone furoate and 25 mcg vilanterol (200/25 mcg) per actuation (3)

---------- CONTRAINDICATIONS ----------

- Primary treatment of status asthmaticus or acute episodes of COPD or asthma requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or any ingredients. (4)

---------- WARNINGS AND PRECAUTIONS----------

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating COPD or asthma. Do not use to treat acute symptoms. (5.2)
- Do not use in combination with additional therapy containing a LABA because of risk of overdose. (5.3)
- *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk. (5.4)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infections; ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. (5.6)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Wean patients slowly from systemic corticosteroids if transferring to BREO ELLIPTA. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue BREO ELLIPTA slowly. (5.8)
- If paradoxical bronchospasm occurs, discontinue BREO ELLIPTA and institute alternative therapy. (5.10)
- Use with caution in patients with cardiovascular disorders because of beta-adrenergic stimulation. (5.12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Monitor growth of pediatric patients (5.14)
- Glaucoma and cataracts may occur with long-term use of ICS. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREO ELLIPTA long term. (5.15)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.16)
- Increased blood glucose levels have been reported. Also, be alert to hypokalemia. (5.17)

---------- ADVERSE REACTIONS ----------

- COPD: Most common adverse reactions (incidence ≥3%) are nasopharyngitis, upper respiratory tract infection, headache, oral candidiasis, back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, and pyrexia. (6.1)
- Asthma: Most common adverse reactions (incidence ≥2%) are nasopharyngitis, oral candidiasis, headache, influenza, upper respiratory tract infection, bronchitis, sinusitis, oropharyngeal pain, dysphonia, and cough. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Use with caution. May cause systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of vilanterol on cardiovascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

---------- USE IN SPECIFIC POPULATIONS ----------

Hepatic impairment: Fluticasone furoate systemic exposure may increase in patients with moderate or severe impairment. Monitor for systemic corticosteroid effects. (8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 05/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

BREO ELLIPTA is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

1.2 Maintenance Treatment of Asthma

BREO ELLIPTA is indicated for the maintenance treatment of asthma in patients aged 5 years and older.

1.3 Limitations of Use

BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Maintenance Treatment of Chronic Obstructive Pulmonary Disease

The recommended dosage of BREO ELLIPTA 100/25 mcg (containing fluticasone furoate 100 mcg and vilanterol 25 mcg) is 1 actuation once daily by oral inhalation.

- If shortness of breath occurs in the period between doses, an inhaled, short-acting beta2-agonist (rescue medicine, e.g., albuterol) should be used for immediate relief.

2.2 Recommended Dosage for Maintenance Treatment of Asthma

Adult Patients Aged 18 Years and Older

The recommended dosage of BREO ELLIPTA 100/25 mcg (containing fluticasone furoate 100 mcg and vilanterol 25 mcg) is 1 actuation once daily by oral inhalation or BREO ELLIPTA

200/25 mcg (containing fluticasone furoate 200 mcg and vilanterol 25 mcg) is 1 actuation once daily by oral inhalation.

- When choosing the starting dosage strength of BREO ELLIPTA, consider the patients' disease severity; their previous asthma therapy, including the inhaled corticosteroid (ICS) dosage; as well as the patients' current control of asthma symptoms and risk of future exacerbation.
- The median time to onset, defined as a 100-mL increase from baseline in mean forced expiratory volume in 1 second (FEV_1), was approximately 15 minutes after beginning treatment. Individual patients will experience a variable time to onset and degree of symptom relief.
- For patients who do not respond adequately to BREO ELLIPTA 100/25 mcg once daily, increasing the dose to BREO ELLIPTA 200/25 mcg once daily may provide additional improvement in asthma control. For patients who do not respond adequately to BREO ELLIPTA 200/25 mcg once daily, re-evaluate and consider other therapeutic regimens and additional therapeutic options.
- The maximum recommended dosage is 1 inhalation of BREO ELLIPTA 200/25 mcg once daily.
- If asthma symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist (rescue medicine, e.g., albuterol) should be used for immediate relief.

Pediatric Patients Aged 12 to 17 Years

The recommended dosage of BREO ELLIPTA 100/25 mcg (containing fluticasone furoate 100 mcg and vilanterol 25 mcg) is 1 actuation once daily by oral inhalation *[see Warnings and Precautions (5.14)]*.

Pediatric Patients Aged 5 to 11 Years

The recommended dosage of BREO ELLIPTA 50/25 mcg (containing fluticasone furoate 50 mcg and vilanterol 25 mcg) is 1 actuation once daily by oral inhalation *[see Warnings and Precautions (5.14)]*.

2.3 Administration Information

- After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis *[see Warnings and Precautions (5.4)]*.
- BREO ELLIPTA should be used at the same time every day. Do not use BREO ELLIPTA more than 1 time every 24 hours.
- More frequent administration or a greater number of inhalations (more than 1 inhalation daily) of the prescribed strength of BREO ELLIPTA is not recommended as some patients are more likely to experience adverse effects with higher doses.

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder:

- 50 mcg fluticasone furoate and 25 mcg vilanterol (50/25 mcg) per actuation
- 100 mcg fluticasone furoate and 25 mcg vilanterol (100/25 mcg) per actuation
- 200 mcg fluticasone furoate and 25 mcg vilanterol (200/25 mcg) per actuation

4 CONTRAINDICATIONS

BREO ELLIPTA is contraindicated in the following conditions:

- Primary treatment of status asthmaticus or other acute episodes of COPD or asthma where intensive measures are required *[see Warnings and Precautions (5.2)]*.
- Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate, vilanterol, or any of the excipients *[see Warnings and Precautions (5.11), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death *[see Salmeterol Multicenter Asthma Research Trial (SMART)]*. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone *(see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists)*.

Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta$_2$-adrenergic Agonists

Four (4) large, 26-week, randomized, double-blind, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in patients with asthma. Three (3) trials included adult and pediatric patients aged 12 years and older: 1 trial compared budesonide/formoterol with budesonide, 1 trial compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder, and 1 trial compared mometasone furoate/formoterol with mometasone furoate. The fourth trial included pediatric patients aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder with fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication

committee determined whether events were asthma related.

The 3 adult and pediatric trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and pediatric trials did not show a significant increase in risk of a serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma Aged 12 Years and Older

	ICS/LABA (n = 17,537)[a]	**ICS (n = 17,552)[a]**	**ICS/LABA vs. ICS Hazard Ratio (95% CI)[b]**
Serious asthma-related event[c]	116	105	1.10 (0.85, 1.44)
Asthma-related death	2	0	
Asthma-related intubation (endotracheal)	1	2	
Asthma-related hospitalization (≥24-hour stay)	115	105	

ICS = Inhaled Corticosteroid, LABA = Long-acting $Beta_2$-adrenergic Agonist.

[a] Randomized patients who had taken at least 1 dose of study drug. Planned treatment used for analysis.

[b] Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

[c] Number of patients with event that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug, whichever date was later. Patients can have one or more events, but only the first event was counted for analysis. A single, blinded, independent adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric patients aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial, 27/3,107 (0.9%) patients randomized to ICS/LABA and 21/3,101 (0.7%) patients randomized to ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations. ICS/LABA did not show a significantly increased risk of a serious asthma-related event compared with ICS based on the pre-specified risk margin (2.7), with an estimated hazard ratio of time to first event of 1.29 (95% CI: 0.73, 2.27).

Salmeterol Multicenter Asthma Research Trial (SMART)

A 28-week, placebo-controlled, U.S. trial that compared the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients

receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). Use of background ICS was not required in SMART. The increased risk of asthma-related death is considered a class effect of LABA monotherapy.

5.2 Deterioration of Disease and Acute Episodes

BREO ELLIPTA should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of COPD or asthma. BREO ELLIPTA has not been studied in patients with acutely deteriorating COPD or asthma. The initiation of BREO ELLIPTA in this setting is not appropriate.

In COPD, if BREO ELLIPTA 100/25 mcg no longer controls symptoms of bronchoconstriction; the patient's inhaled, short-acting, beta$_2$-agonist becomes less effective; or the patient needs more short-acting beta$_2$-agonist than usual, these may be markers of deterioration of disease. In this setting, re-evaluate the patient and the COPD treatment regimen at once. For COPD, the daily dose of BREO ELLIPTA 100/25 mcg should not be increased.

Increasing use of inhaled, short-acting beta$_2$-agonists is a marker of deteriorating asthma. In this situation, the patient requires immediate reevaluation with reassessment of the treatment regimen, giving special consideration to the need for additional therapeutic options. Patients should not use more than 1 inhalation once daily of BREO ELLIPTA.

BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. BREO ELLIPTA has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist.

When beginning treatment with BREO ELLIPTA, patients who have been taking oral or inhaled, short-acting beta$_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs and to use them only for symptomatic relief of acute respiratory symptoms. When prescribing BREO ELLIPTA, the healthcare provider should also prescribe an inhaled, short-acting beta$_2$-agonist and instruct the patient on how it should be used.

5.3 Risk Associated with Excessive Use of Long-acting Beta$_2$-agonists, including BREO ELLIPTA

BREO ELLIPTA should not be used more often than recommended, at higher doses than recommended *[see Dosage and Administration (2)]*, or in conjunction with other therapies 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 therapy containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

5.4 Oropharyngeal Candidiasis

BREO ELLIPTA contains fluticasone furoate, an ICS. Localized infections of the mouth and pharynx with *Candida albicans* have occurred in patients treated with orally inhaled drug products containing fluticasone furoate. Monitor patients periodically. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with BREO ELLIPTA continues. In some cases, therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following administration of BREO ELLIPTA to help reduce the risk of oropharyngeal candidiasis.

5.5 Pneumonia

An increase in the incidence of pneumonia has been observed in patients with COPD receiving BREO ELLIPTA 100/25 mcg in clinical trials. There was also an increased incidence of pneumonias resulting in hospitalization. In some incidences these pneumonia events were fatal. Healthcare providers should remain vigilant for the possible development of pneumonia in patients with COPD as clinical features of pneumonia and exacerbations frequently overlap.

In replicate 12-month trials in 3,255 patients with moderate to severe COPD who had experienced a COPD exacerbation in the previous year, there was a higher incidence of pneumonia reported in patients receiving fluticasone furoate/vilanterol 50/25 mcg: 6% (48 of 820 patients); BREO ELLIPTA 100/25 mcg: 6% (51 of 806 patients); or BREO ELLIPTA 200/25 mcg: 7% (55 of 811 patients) than in patients receiving vilanterol 25 mcg: 3% (27 of 818 patients). There was no fatal pneumonia in patients receiving vilanterol or fluticasone furoate/vilanterol 50/25 mcg. There was fatal pneumonia in 1 patient receiving BREO ELLIPTA 100/25 mcg and in 7 patients receiving BREO ELLIPTA 200/25 mcg (<1% for each treatment group).

In a mortality trial with a median treatment duration of 1.5 years in 16,568 patients with moderate COPD and cardiovascular disease, the annualized incidence rate of pneumonia was 3.4 per 100 patient-years for BREO ELLIPTA 100/25 mcg, 3.2 for placebo, 3.3 for fluticasone furoate 100 mcg, and 2.3 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to pneumonia occurred in 13 patients receiving BREO ELLIPTA 100/25 mcg, 9 patients receiving placebo, 10 patients receiving fluticasone furoate 100 mcg, and 6 patients receiving vilanterol 25 mcg (<0.2 per 100 patient-years for each treatment group).

5.6 Immunosuppression and Risk of Infections

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles can have a more serious or even fatal course in susceptible patients using corticosteroids. In such patients who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated

infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective Prescribing Information for VZIG and IG) If chickenpox develops, treatment with antiviral agents may be considered.

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

5.7 Transferring Patients from Systemic Corticosteroid Therapy

HPA Suppression/Adrenal Insufficiency

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer from systemic corticosteroids to less systemically available ICS. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although BREO ELLIPTA may control COPD or asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress, a severe COPD exacerbation, or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their healthcare practitioner for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress, a severe COPD exacerbation, or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to BREO ELLIPTA. Prednisone reduction can be accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy with BREO ELLIPTA. Lung function (FEV_1 or peak expiratory flow), beta-agonist use, and COPD or asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition, patients

should be observed for signs and symptoms of adrenal insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Unmasking of Allergic Conditions Previously Suppressed by Systemic Corticosteroids

Transfer of patients from systemic corticosteroid therapy to BREO ELLIPTA may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy (e.g., rhinitis, conjunctivitis, eczema, arthritis, eosinophilic conditions).

Corticosteroid Withdrawal Symptoms

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal (e.g., joint and/or muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.8 Hypercorticism and Adrenal Suppression

Inhaled fluticasone furoate is absorbed into the circulation and can be systemically active. Effects of fluticasone furoate on the HPA axis are not observed with the therapeutic doses of fluticasone furoate in BREO ELLIPTA. However, exceeding the recommended dosage or coadministration with a strong cytochrome P450 3A4 (CYP3A4) inhibitor may result in HPA dysfunction *[see Warnings and Precautions (5.9), Drug Interactions (7.1)]*.

Because of the possibility of significant systemic absorption of ICS in sensitive patients, patients treated with BREO ELLIPTA should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients who are sensitive to these effects. If such effects occur, reduce the dose of BREO ELLIPTA slowly, consistent with accepted procedures for reducing systemic corticosteroids, and consider other treatments for management of COPD or asthma symptoms.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of BREO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors (including, but not limited to, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.10 Paradoxical Bronchospasm

BREO ELLIPTA can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with BREO ELLIPTA, it should be treated immediately with an inhaled, short-acting bronchodilator; BREO ELLIPTA should be

discontinued immediately; and alternative therapy should be instituted *[see Adverse Reactions (6.3)]*.

5.11 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions such as anaphylaxis, angioedema, rash, and urticaria may occur after administration of BREO ELLIPTA. Discontinue BREO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO ELLIPTA *[see Contraindications (4), Adverse Reactions (6.3)]*.

5.12 Cardiovascular Effects

BREO ELLIPTA, like other drugs containing beta$_2$-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles *[see Adverse Reactions (6.3)]*. If such effects occur, BREO ELLIPTA may need to be discontinued. In addition, beta-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 *[see Clinical Pharmacology (12.2)]*. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

In healthy subjects, large doses of inhaled fluticasone furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12- or 10-fold higher systemic exposure than seen in patients with COPD or asthma, respectively) have been associated with clinically significant prolongation of the QTc interval, which has the potential for producing ventricular arrhythmias. Therefore, BREO ELLIPTA, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

In a mortality trial with a median treatment duration of 1.5 years in 16,568 patients with moderate COPD and cardiovascular disease, the annualized incidence rate of adjudicated cardiovascular events (composite of myocardial infarction, stroke, unstable angina, transient ischemic attack, or on-treatment death due to cardiovascular events) was 2.5 per 100 patient-years for BREO ELLIPTA 100/25 mcg, 2.7 for placebo, 2.4 for fluticasone furoate 100 mcg, and 2.6 for vilanterol 25 mcg. Adjudicated, on-treatment deaths due to cardiovascular events occurred in 82 patients receiving BREO ELLIPTA 100/25 mcg, 86 patients receiving placebo, 80 patients receiving fluticasone furoate 100 mcg, and 90 patients receiving vilanterol 25 mcg (annualized incidence rate ranged from 1.2 to 1.3 per 100 patient-years for the treatment groups).

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing ICS. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care. Since patients with COPD often have multiple risk factors for reduced BMD, assessment of BMD is recommended prior to initiating BREO ELLIPTA and periodically thereafter. If significant reductions in BMD are seen and BREO ELLIPTA is still considered medically important for that patient's COPD therapy, use of therapy to treat or prevent osteoporosis should be strongly considered.

In replicate 12-month trials in 3,255 patients with moderate to severe COPD, bone fractures were reported by 2% of patients receiving the fluticasone furoate/vilanterol combination (50/25 mcg: 2% [14 of 820 patients]; 100/25 mcg: 2% [19 of 806 patients]; or 200/25 mcg: 2% [14 of 811 patients]) compared with <1% of patients receiving vilanterol 25 mcg alone (8 of 818 patients).

Similar findings were seen in a mortality trial with a median treatment duration of 1.5 years in 16,568 patients with moderate COPD and cardiovascular disease.

5.14 Effect on Growth

Orally inhaled corticosteroids, , including fluticasone furoate, a component in BREO ELLIPTA may cause a reduction in growth velocity when administered to pediatric patients. The safety and effectiveness of BREO ELLIPTA have not been established in pediatric patients less than 5 years of age. Monitor the growth of pediatric patients receiving BREO ELLIPTA routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including BREO ELLIPTA, titrate each patient's dose to the lowest dosage that effectively controls his/her symptoms *[see Dosage and Administration (2.3), Use in Specific Populations (8.4)]*.

5.15 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of ICS, including fluticasone furoate, a component in BREO ELLIPTA. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREO ELLIPTA long term.

5.16 Risk of Using Sympathomimetic Amines in Certain Coexisting Conditions

BREO ELLIPTA, like all therapies containing sympathomimetic amines, should be used with caution in patients with convulsive disorders, thyrotoxicosis, or diabetes mellitus and in those who are unusually responsive to sympathomimetic amines. Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.17 Hyperglycemia and Hypokalemia

There have been reports of increases in blood glucose levels with BREO ELLIPTA. This should be considered in patients with a history of, or with risk factors for, diabetes mellitus *[see Adverse Reactions (6.3)]*.

Beta-adrenergic agonist therapies may produce significant hypokalemia 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. In clinical trials evaluating BREO ELLIPTA in patients with COPD or asthma, there was no evidence of a treatment effect on serum potassium.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Serious Asthma-Related Events – Hospitalizations, Intubations, Death *[see Warnings and Precautions (5.1)]*
- Oropharyngeal Candidiasis *[see Warnings and Precautions (5.4)]*
- Pneumonia *[see Warnings and Precautions (5.5)]*
- Immunosuppression and Risk of Infections *[see Warnings and Precautions (5.6)]*
- Hypercorticism and Adrenal Suppression *[see Warnings and Precautions (5.8)]*
- Paradoxical Bronchospasm *[see Warnings and Precautions (5.10)]*
- Cardiovascular Effects *[see Warnings and Precautions (5.12)]*
- Reduction in Bone Mineral Density *[see Warnings and Precautions (5.13)]*
- Growth Effects *[see Warnings and Precautions (5.14)]*
- Glaucoma and Cataracts *[see Warnings and Precautions (5.15)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience in Chronic Obstructive Pulmonary Disease

The safety data described below are based on two 6-month and two 12-month trials and one long-term mortality trial. In these studies, 5,356 patients with COPD received at least 1 dose of BREO ELLIPTA 100/25 mcg. Adverse reactions observed in other studies of BREO ELLIPTA in COPD patients were similar to those observed in these 5 trials.

6-Month Trials

The incidence of adverse reactions associated with BREO ELLIPTA 100/25 mcg in Table 2 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n = 1,224 and n = 1,030,

respectively). Of the 2,254 patients, 70% were male and 84% were White. They had a mean age of 62 years and an average smoking history of 44 pack years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), the mean postbronchodilator FEV_1/forced vital capacity (FVC) ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%).

Patients received 1 inhalation once daily of the following: BREO ELLIPTA 100/25 mcg, BREO ELLIPTA 200/25 mcg, fluticasone furoate/vilanterol 50/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or placebo.

Table 2. Adverse Reactions with BREO ELLIPTA 100/25 mcg with ≥3% Incidence and More Common than Placebo in Patients with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BREO ELLIPTA 100/25 mcg (n = 410) %	Vilanterol 25 mcg (n = 408) %	Fluticasone Furoate 100 mcg (n = 410) %	Placebo (n = 412) %
Infections and infestations				
Nasopharyngitis	9	10	8	8
Upper respiratory tract infection	7	5	4	3
Oropharyngeal candidiasis[a]	5	2	3	2
Nervous system disorders				
Headache	7	9	7	5

[a] Includes oral candidiasis, oropharyngeal candidiasis, candidiasis, and fungal oropharyngitis.

12-Month Trials

Long-term safety data are based on two 12-month trials (Trials 3 and 4; n = 1,633 and n = 1,622, respectively). Trials 3 and 4 included 3,255 patients, of which 57% were male and 85% were White. They had a mean age of 64 years and an average smoking history of 46 pack years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and the mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the patient population had moderate to very severely impaired airflow obstruction. Patients received 1 inhalation once daily of the following: BREO ELLIPTA 100/25 mcg, BREO ELLIPTA 200/25 mcg, fluticasone furoate/vilanterol 50/25 mcg, or vilanterol 25 mcg. In addition to the reactions shown in Table 2, adverse reactions occurring in ≥3% of the patients treated with BREO ELLIPTA 100/25 mcg (n = 806) for 12 months included back pain, pneumonia *[see Warnings and Precautions (5.5)]*, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, influenza, pharyngitis, and pyrexia.

Mortality Trial

Safety data are available from a mortality trial in patients with moderate COPD (moderate airflow limitation [≥50% and ≤70% predicted FEV_1]) who either had a history of, or were at risk of, cardiovascular disease and were treated for up to 4 years (median treatment duration of 1.5 years). The trial included 16,568 patients, 4,140 of whom received BREO ELLIPTA 100/25 mcg. In addition to the events in COPD trials shown in Table 2, adverse reactions occurring in ≥3% of the patients treated with BREO ELLIPTA 100/25 mcg and more common than placebo included pneumonia, back pain, hypertension, and influenza.

6.2 Clinical Trials Experience in Asthma

The safety data described below was based on trials that evaluated of BREO ELLIPTA 100/25 mcg in 1,757 patients and BREO ELLIPTA 200/25 mcg in 745 patients. While patients aged 12 to 17 years were included in these trials, BREO ELLIPTA 200/25 mcg is not approved for use in this age group *[see Dosage and Administration (2.3)]*.

One additional 24-week trial enrolled 902 pediatric patients with asthma. In this trial, BREO ELLIPTA 100/25 mcg was studied in 117 patients aged 12 to 17 years and BREO ELLIPTA 50/25 mcg was studied in 337 patients aged 5 to 11 years.

Adult Patients

The safety of BREO ELLIPTA for the maintenance treatment of asthma in adult patients was based on the data from Trials 8, 9, 10, 11 and 12 *[see Clinical Studies (14.2)]*. Trial 8 was a 12-week trial that evaluated the efficacy of BREO ELLIPTA 100/25 mcg in patients with asthma compared with fluticasone furoate 100 mcg and placebo. The incidence of adverse reactions associated with BREO ELLIPTA 100/25 mcg is shown in Table 3.

Table 3. Adverse Reactions with BREO ELLIPTA 100/25 mcg with ≥2% Incidence and More Common than Placebo in Patients with Asthma (Trial 8)

Adverse Reaction	BREO ELLIPTA 100/25 mcg (n = 201) %	Fluticasone Furoate 100 mcg (n = 205) %	Placebo (n = 203) %
Infections and infestations			
Nasopharyngitis	10	7	7
Oral candidiasis[a]	2	2	0
Nervous system disorders			
Headache	5	4	4
Respiratory, thoracic, and mediastinal disorders			
Oropharyngeal pain	2	2	1
Dysphonia	2	1	0

[a] Includes oral candidiasis and oropharyngeal candidiasis.

Trial 9 was a 12-week trial that evaluated the efficacy of BREO ELLIPTA 100/25 mcg, BREO ELLIPTA 200/25 mcg, and fluticasone furoate 100 mcg in patients with asthma. This trial did not have a placebo arm. The incidence of adverse reactions associated with BREO ELLIPTA 100/25 mcg and BREO ELLIPTA 200/25 mcg is shown in Table 4.

Table 4. Adverse Reactions with BREO ELLIPTA 100/25 mcg and BREO ELLIPTA 200/25 mcg with ≥2% Incidence in Patients with Asthma (Trial 9)

Adverse Reaction	BREO ELLIPTA 200/25 mcg (n = 346) %	BREO ELLIPTA 100/25 mcg (n = 346) %	Fluticasone Furoate 100 mcg (n = 347) %
Nervous system disorders			
Headache	8	8	9
Infections and infestations			
Nasopharyngitis	7	6	7
Influenza	3	3	1
Upper respiratory tract infection	2	2	3
Sinusitis	2	1	<1
Bronchitis	2	<1	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	2	1
Cough	1	2	1

24-Week Trial

Trial 10 was a 24-week trial that evaluated the efficacy of BREO ELLIPTA 200/25 mcg once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in patients with asthma. This trial did not have a placebo arm. In addition to the reactions shown in Tables 3 and 4, adverse reactions occurring in ≥2% of patients treated with BREO ELLIPTA 200/25 mcg included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.

12-Month Trial

Long-term safety data are based on a 12-month trial that evaluated the safety of BREO ELLIPTA 100/25 mcg once daily (n = 201), BREO ELLIPTA 200/25 mcg once daily (n = 202), and fluticasone propionate 500 mcg twice daily (n = 100) in patients with asthma (Trial 11). In addition to the reactions shown in Tables 3 and 4, adverse reactions occurring in ≥2% of the patients treated with BREO ELLIPTA 100/25 mcg or BREO ELLIPTA 200/25 mcg for 12 months included pyrexia, back pain, extrasystoles, upper abdominal pain, respiratory tract infection, allergic rhinitis, pharyngitis, rhinitis, arthralgia, supraventricular extrasystoles, ventricular extrasystoles, acute sinusitis, and pneumonia.

Adult and Pediatric Patients Aged 12 to 17 Years Exacerbation Trial

Trial 12 included both adult and pediatric patients 12 years of age and older. Although this trial did not support efficacy of BREO ELLIPTA for maintenance treatment of asthma in pediatric

patients 12 to 17 years of age, it was used to evaluate safety in both adult and pediatric patients 12 to 17 years of age. Patients received BREO ELLIPTA 100/25 mcg (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Patients participating in this trial had a history of 1 or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry. Asthma-related hospitalizations occurred in 10 patients (1%) treated with BREO ELLIPTA 100/25 mcg compared with 7 patients (0.7%) treated with fluticasone furoate 100 mcg. Among patients aged 12 to 17 years, asthma-related hospitalizations occurred in 4 patients (2.6%) treated with BREO ELLIPTA 100/25 mcg (n = 151) compared with 0 patients treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related intubations observed in this trial.

Pediatric Patients Aged 5 to 17 Years

The safety of BREO ELLIPTA for the maintenance treatment of asthma in pediatric patients 5 years and older was based on the data from Trial 14, a 24-week clinical trial that enrolled 902 patients with asthma aged 5 to 17 years (aged 5 to 11 years [n = 673]; aged 12 to 17 years [n = 229]). Pediatric patients aged 12 to 17 years were randomized to BREO ELLIPTA 100/25 mcg (n = 117) or fluticasone furoate 100 mcg (n = 112). Pediatric patients aged 5 to 11 years were randomized to BREO ELLIPTA 50/25 mcg (n = 337) or fluticasone furoate 50 mcg (n = 336) *[see Clinical Studies (14.2)]*. Adverse reactions reported in ≥3% of pediatric patients treated with BREO ELLIPTA is shown in Table 5.

Table 5. Adverse Reactions with BREO ELLIPTA with ≥3% Incidence in Pediatric Patients with Asthma (Trial 14)

Adverse Reaction	BREO ELLIPTA[a] (n = 454) %	Fluticasone Furoate[b] (n = 448) %
Infections and infestations		
Nasopharyngitis	10	8
Upper respiratory tract infection	7	6
Rhinitis	3	1
Viral upper respiratory tract infection	3	<1
Respiratory, thoracic and mediastinal disorders		
Rhinitis allergic	4	1
Nervous system disorders		
Headache	3	2

[a] The dose of BREO ELLIPTA was 100/25 mcg once daily for pediatric patients aged 12 to 17 years and 50/25 mcg once daily for pediatric patients aged 5 to 11 years.

[b] The dose of fluticasone furoate was 100 mcg once daily for pediatric patients aged 12 to 17 years and 50 mcg once daily for pediatric patients aged 5 to 11 years.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of BREO ELLIPTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to BREO ELLIPTA or a combination of these factors.

Cardiac Disorders

Palpitations, tachycardia.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria.

Metabolism and Nutrition Disorders

Hyperglycemia.

Musculoskeletal and Connective Tissue Disorders

Muscle spasms.

Nervous System Disorders

Tremor.

Psychiatric Disorders

Nervousness.

Respiratory, Thoracic, and Mediastinal Disorders

Paradoxical bronchospasm.

7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol are both substrates of CYP3A4. Concomitant administration of the strong CYP3A4 inhibitor ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution should be exercised when considering the coadministration of BREO ELLIPTA with ketoconazole and other known strong CYP3A4 inhibitors *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3)]*.

7.2 Monoamine Oxidase Inhibitors, Tricyclic Antidepressants, and QTc Prolonging Drugs

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 or within 2 weeks of discontinuation of such agents, 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.

7.3 Beta-adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, but may also produce severe bronchospasm in patients with COPD or asthma. Therefore, patients with COPD or asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-blockers could be considered, although they should be administered with caution.

7.4 Non–Potassium-Sparing Diuretics

The electrocardiographic changes and/or hypokalemia that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non–potassium-sparing diuretics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are insufficient data on the use of BREO ELLIPTA or its individual components, fluticasone furoate and vilanterol, in pregnant women to inform a drug-associated risk. *(See Clinical Considerations.)* In an animal reproduction study, fluticasone furoate and vilanterol administered by inhalation alone or in combination to pregnant rats during the period of organogenesis produced no fetal structural abnormalities. The highest fluticasone furoate and vilanterol doses in this study were approximately 5 and 40 times the maximum recommended human daily inhalation doses (MRHDID) of 200 and 25 mcg, respectively. *(See Data.)*

The estimated risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal outcomes such as pre-eclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control of asthma.

Labor or Delivery: BREO ELLIPTA should be used during late gestation and labor only if the potential benefit justifies the potential for risks related to beta-agonists interfering with uterine contractility.

Data

Animal Data: Fluticasone Furoate and Vilanterol: In an embryofetal developmental study, pregnant rats received fluticasone furoate and vilanterol during the period of organogenesis at doses up to approximately 5 and 40 times the MRHDID of 200 and 25 mcg, respectively, alone or in combination (on a mcg/m^2 basis at inhalation doses up to approximately 95 mcg/kg/day). No evidence of structural abnormalities was observed.

Fluticasone Furoate: In 2 separate embryofetal developmental studies, pregnant rats and rabbits received fluticasone furoate during the period of organogenesis at doses up to approximately 4 and 1 times, respectively, the MRHDID of 200 mcg (on a mcg/m^2 basis at maternal inhalation doses up to 91 and 8 mcg/kg/day, respectively). No evidence of structural abnormalities in fetuses was observed in either species. In a perinatal and postnatal developmental study in rats, dams received fluticasone furoate during late gestation and lactation periods at doses up to approximately 1 time the MRHDID of 200 mcg (on a mcg/m^2 basis at maternal inhalation doses up to 27 mcg/kg/day). No evidence of effects on offspring development was observed.

Vilanterol: In 2 separate embryofetal developmental studies, pregnant rats and rabbits received vilanterol during the period of organogenesis at doses up to approximately 13,000 and 1,000 times, respectively, the MRHDID (on a mcg/m^2 basis at maternal inhalation doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 5,740 mcg/kg/day in rabbits). No evidence of structural abnormalities was observed at any dose in rats or in rabbits up to approximately 160 times the MRHDID (on an AUC basis at maternal doses up to 591 mcg/kg/day). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID (on an AUC basis at maternal inhaled or subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included decreased or absent ossification in cervical vertebral centrum and metacarpals. In a perinatal and postnatal developmental study in rats, dams received vilanterol during late gestation and the lactation periods at doses up to approximately 3,900 times the MRHDID (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day). No evidence of effects in offspring development was observed.

8.2 Lactation

Risk Summary

There is no information available on the presence of fluticasone furoate or vilanterol in human milk, the effects on the breastfed child, or the effects on milk production. Low concentrations of other ICS have been detected in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BREO ELLIPTA and any potential adverse effects on the breastfed child from fluticasone furoate or vilanterol or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of BREO ELLIPTA for the maintenance treatment of asthma in pediatric patients 5 years of age and older have been established. This indication is based on Trial 14, an adequate and well-controlled trial in pediatric patients aged 5 to 17 years *[see Adverse Reactions (6.2) and Clinical Studies (14.2)]*. The recommended dosage for pediatric patients is different than the adult dosage *[see Dosage and Administration (2.2)]*.

The safety and efficacy of BREO ELLIPTA in pediatric patients aged younger than 5 years have not been established.

In Trial 12, an exacerbation trial *[see Clinical Studies (14.2)]*, pediatric patients aged 12 to 17 years (n = 281) were treated with BREO ELLIPTA 100/25 mcg (n = 151) or treated with fluticasone furoate 100 mcg (n = 130). Among these patients, 10% of patients treated with BREO ELLIPTA 100/25 mcg reported an asthma exacerbation compared with 7% for patients treated with fluticasone furoate 100 mcg. Asthma-related hospitalizations occurred in 4 patients (2.6%) treated with BREO ELLIPTA 100/25 mcg compared with 0 patients treated with fluticasone furoate 100 mcg.

Effects on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. A reduction of growth velocity in pediatric patients may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of pediatric patients with ICS, including fluticasone furoate, on final adult height are not known.

Controlled clinical trials have shown that ICS may cause a reduction in growth in children. In these trials, the mean reduction in growth velocity was approximately 1 cm/year (range: 0.3 to 1.8 cm/year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with

orally inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving orally inhaled corticosteroids, including BREO ELLIPTA, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including BREO ELLIPTA, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A randomized, double blind, parallel-group, multicenter, 1-year, placebo-controlled trial evaluated the effect of once-daily treatment with orally inhaled fluticasone furoate 50 mcg on growth velocity assessed by stadiometry. The patients were 457 prepubertal children (girls aged 5 to <8 years and boys aged 5 to <9 years). Mean growth velocity over the 52-week treatment period was lower in the patients receiving orally inhaled fluticasone furoate (5.905 cm/year) compared with placebo (6.065 cm/year). The mean reduction in growth velocity was 0.16 cm/year (95% CI: - 0.14, 0.46) *[see Warnings and Precautions (5.14)]*.

8.5 Geriatric Use

Based on available data, no adjustment of the dosage of BREO ELLIPTA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Clinical trials of BREO ELLIPTA for COPD included 4,820 subjects aged 65 years and older and 1,118 subjects aged 75 years and older. Clinical trials of BREO ELLIPTA for asthma included 854 subjects aged 65 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Hepatic Impairment

Fluticasone furoate systemic exposure increased by up to 3-fold in adult patients with hepatic impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol systemic exposure. Use BREO ELLIPTA with caution in patients with moderate or severe hepatic impairment. Monitor patients for corticosteroid-related side effects. The effect of hepatic impairment on fluticasone furoate and vilanterol systemic exposure in patients aged younger than 18 years has not been evaluated *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

There were no significant increases in either fluticasone furoate or vilanterol exposure in patients with severe renal impairment (CrCl <30 mL/min) compared with healthy subjects. No dosage adjustment is required in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

BREO ELLIPTA contains both fluticasone furoate and vilanterol; therefore, the risks associated with overdosage for the individual components described below apply to BREO ELLIPTA. Treatment of overdosage consists of discontinuation of BREO ELLIPTA together with

institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

Fluticasone Furoate

Because of low systemic bioavailability (15.2%) and an absence of acute drug-related systemic findings in clinical trials, overdosage of fluticasone furoate is unlikely to require any treatment other than observation. If used at excessive doses for prolonged periods, systemic effects such as hypercorticism may occur *[see Warnings and Precautions (5.8)]*.

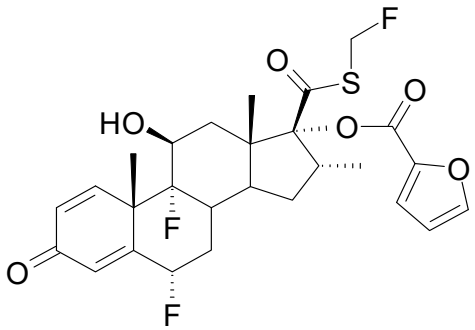
Vilanterol

The expected signs and symptoms with overdosage of vilanterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of vilanterol.

11 DESCRIPTION

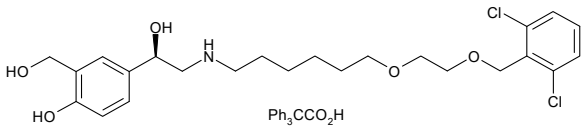
BREO ELLIPTA is an inhalation powder drug product for delivery of a combination of fluticasone furoate (an ICS) and vilanterol (a LABA) to patients by oral inhalation.

Fluticasone furoate, a synthetic trifluorinated corticosteroid, has the chemical name (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate and the following chemical structure:



Fluticasone furoate is a white powder with a molecular weight of 538.6, and the empirical formula is $C_{27}H_{29}F_3O_6S$. It is practically insoluble in water.

Vilanterol trifenatate has the chemical name triphenylacetic acid-4-{(1*R*)-2-[(6-{2-[2,6-dicholorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1) and the following chemical structure:



Vilanterol trifenatate is a white powder with a molecular weight of 774.8, and the empirical formula is $C_{24}H_{33}Cl_2NO_5 \bullet C_{20}H_{16}O_2$. It is practically insoluble in water.

BREO ELLIPTA is a light grey and pale blue plastic inhaler containing 2 foil blister strips. Each blister on one strip contains a white powder blend of micronized fluticasone furoate (50, 100, or 200 mcg) and lactose monohydrate (12.5, 12.4 or 12.3 mg, respectively), and each blister on the other strip contains a white powder blend of micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate (125 mcg), and lactose monohydrate (12.34 mg). The lactose monohydrate contains milk proteins. After the inhaler is activated, the powder within both blisters is exposed and ready for dispersion into the airstream created by the patient inhaling through the mouthpiece.

Under standardized in vitro test conditions, BREO ELLIPTA delivers 46, 92 or 184 mcg of fluticasone furoate and 22 mcg of vilanterol per dose when tested at a flow rate of 60 L/min for 4 seconds.

In adult patients with obstructive lung disease and severely compromised lung function (COPD with FEV_1/FVC <70% and FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure), mean peak inspiratory flow through the ELLIPTA inhaler was 66.5 L/min (range: 43.5 to 81.0 L/min).

In adult patients with severe asthma, mean peak inspiratory flow through the ELLIPTA inhaler was 96.6 L/min (range: 72.4 to 124.6 L/min). In pediatric patients with asthma aged 5 to 11 years, mean peak inspiratory flow through the ELLIPTA inhaler was 60.6 L/min (range: 36.3 to 82.5 L/min).

The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BREO ELLIPTA

BREO ELLIPTA contains both fluticasone furoate and vilanterol. The mechanisms of action described below for the individual components apply to BREO ELLIPTA. These drugs represent 2 different classes of medications (an ICS and a LABA), each having different effects on clinical and physiological indices.

Fluticasone Furoate

Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor that is approximately 29.9 times that of dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these findings is unknown.

The precise mechanism through which fluticasone furoate affects COPD and asthma symptoms is not known. Inflammation is an important component in the pathogenesis of COPD and asthma. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as NFkB, and inhibition of antigen-induced lung eosinophilia in sensitized rats. These anti-inflammatory actions of corticosteroids may contribute to their efficacy.

Vilanterol

Vilanterol is a LABA. In vitro tests have shown the functional selectivity of vilanterol was similar to salmeterol. The clinical relevance of this in vitro finding is unknown.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenergic agonist drugs, including vilanterol, are at least in part attributable to stimulation of intracellular adenyl 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Healthy Subjects: QTc interval prolongation was studied in a double-blind, multiple-dose, placebo- and positive-controlled crossover study in 85 healthy volunteers. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 4.9 (7.5) milliseconds and 9.6 (12.2) milliseconds seen 30 minutes after dosing for fluticasone furoate/vilanterol 200/25 mcg and fluticasone furoate/vilanterol 800/100 mcg, respectively.

A dose-dependent increase in heart rate was also observed. The maximum mean (95% upper confidence bound) difference in heart rate from placebo after baseline correction was

7.8 (9.4) beats/min and 17.1 (18.7) beats/min seen 10 minutes after dosing for fluticasone furoate/vilanterol 200/25 mcg and fluticasone furoate/vilanterol 800/100 mcg, respectively.

Hypothalamic-Pituitary-Adrenal Axis Effects

Healthy Subjects: Inhaled fluticasone furoate at repeat doses up to 400 mcg was not associated with statistically significant decreases in serum or urinary cortisol in healthy subjects. Decreases in serum and urine cortisol levels were observed at fluticasone furoate exposures several-fold higher than exposures observed at the therapeutic dose.

Patients with Chronic Obstructive Pulmonary Disease: In a trial with patients with COPD, treatment with fluticasone furoate (50, 100, or 200 mcg)/vilanterol 25 mcg, vilanterol 25 mcg, or fluticasone furoate (100 or 200 mcg) for 6 months did not affect 24-hour urinary cortisol excretion. A separate trial with patients with COPD demonstrated no effects on serum cortisol after 28 days of treatment with fluticasone furoate (50, 100, or 200 mcg)/vilanterol 25 mcg.

Patients with Asthma: A randomized, double-blind, parallel-group trial in 104 pediatric patients with asthma (aged 5 to 11 years) showed no difference between once-daily treatment with inhaled fluticasone furoate 50 mcg compared with placebo on serum cortisol weighted mean (0 to 24 hours) and serum cortisol $AUC_{(0\text{-}24)}$ following 6 weeks of treatment.

A randomized, double-blind, parallel-group trial in 185 patients with asthma aged 12 to 65 years showed no difference between once-daily treatment with fluticasone furoate/vilanterol 100/25 mcg or fluticasone furoate/vilanterol 200/25 mcg compared with placebo on serum cortisol weighted mean (0 to 24 hours), serum cortisol $AUC_{(0\text{-}24)}$, and 24-hour urinary cortisol after 6 weeks of treatment, whereas prednisolone 10 mg given once daily for 7 days resulted in significant cortisol suppression.

12.3 Pharmacokinetics

Linear pharmacokinetics was observed for fluticasone furoate (200 to 800 mcg) and vilanterol (25 to 100 mcg). On repeated once-daily inhalation administration, steady state of fluticasone furoate and vilanterol plasma concentrations was achieved after 6 days, and the accumulation was up to 2.6-fold for fluticasone furoate and 2.4-fold for vilanterol as compared with single dose.

Absorption

Fluticasone Furoate: Fluticasone furoate plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 0.5 to 1 hour. Absolute bioavailability of fluticasone furoate when administered by inhalation was 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose is low (approximately 1.3%) due to extensive first-pass metabolism. Systemic exposure (AUC) in patients with COPD or asthma was 46% or 7% lower, respectively, than observed in healthy subjects.

Vilanterol: Vilanterol plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 10 minutes following inhalation. Absolute bioavailability of vilanterol when administered by inhalation was 27.3%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose of vilanterol is low (<2%) due to extensive first-pass metabolism. Systemic exposure (AUC) in patients with COPD was 24% higher than observed in healthy subjects. Systemic exposure (AUC) in patients with asthma was 21% lower than observed in healthy subjects.

Distribution

Fluticasone Furoate: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 661 L. Binding of fluticasone furoate to human plasma proteins was high (>99%).

Vilanterol: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165 L. Binding of vilanterol to human plasma proteins was on average 94%.

Elimination

Metabolism: Fluticasone Furoate: Fluticasone furoate is cleared from systemic circulation principally by hepatic metabolism via CYP3A4 to metabolites with significantly reduced corticosteroid activity. There was no in vivo evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.

Vilanterol: Vilanterol is mainly metabolized, principally via CYP3A4, to a range of metabolites with significantly reduced β_1- and β_2-agonist activity.

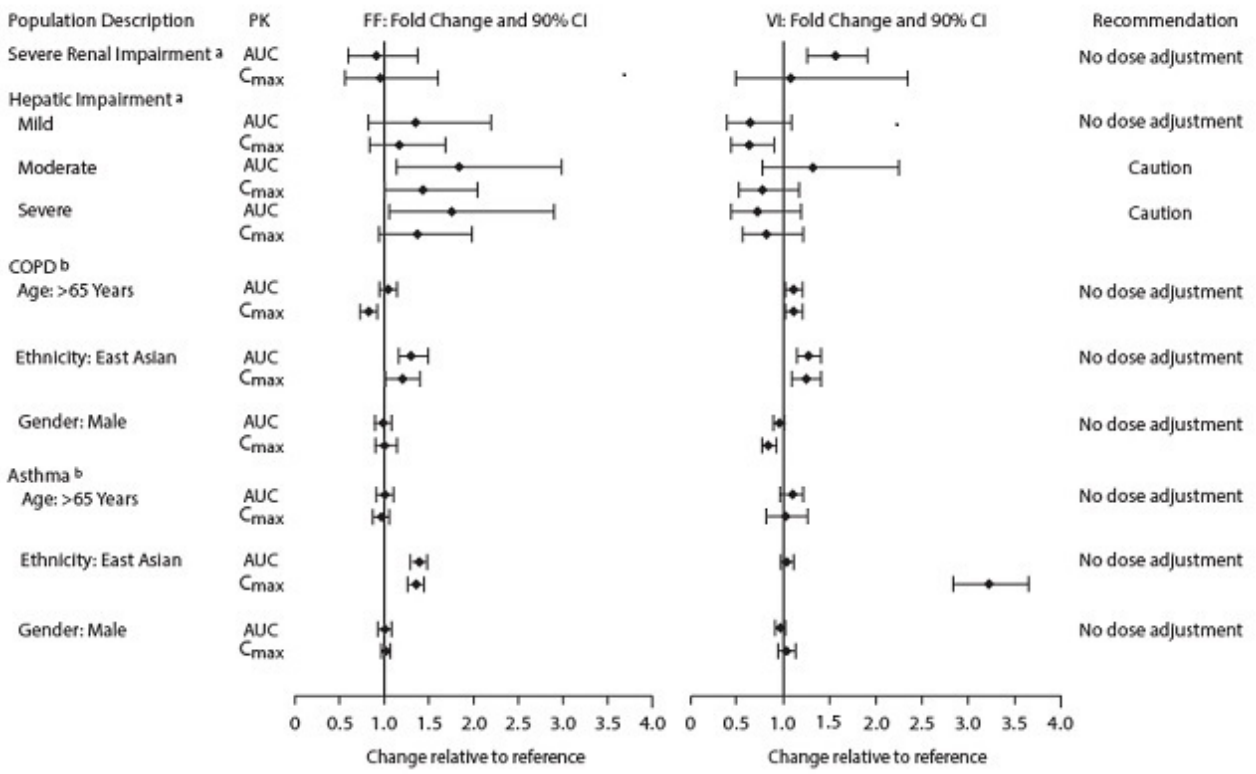
Excretion: Fluticasone Furoate: Fluticasone furoate and its metabolites are eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and intravenously administered doses, respectively. Urinary excretion accounted for approximately 1% and 2% of the orally and intravenously administered doses, respectively. Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

Vilanterol: Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and feces (approximately 70% and 30%, respectively, of the recovered radioactive dose). The plasma elimination half-life of vilanterol, as determined from inhalation administration of multiple doses of vilanterol 25 mcg, is 21.3 hours in patients with COPD and 16.0 hours in patients with asthma.

Specific Populations

The effects of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of fluticasone furoate and vilanterol are shown in Figure 1.

Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Fluticasone Furoate (FF) and Vilanterol (VI) Following Administration as Fluticasone Furoate/Vilanterol Combination



[a] Severe renal impairment (CrCl <30 mL/min) compared with healthy subjects; mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with healthy subjects.

[b] For COPD and asthma, the following comparisons were made: age compared with ≤65 years, gender compared with female, and ethnicity compared with White.

Pediatric Patients: Fluticasone Furoate: A population pharmacokinetics analysis to assess impact of age on fluticasone furoate systemic exposure was conducted using combined data from clinical trials in pediatric patients aged 5 to 11 years (n = 306). There was no relevant effect of age on the apparent clearance of fluticasone furoate. The dose-adjusted fluticasone furoate systemic exposure at steady state in children aged 5 to 11 years following 50 mcg were comparable to that observed in adult and pediatric patients 12 years and older following dosing with fluticasone furoate 100 mcg monotherapy.

Vilanterol: A population pharmacokinetic analysis was conducted to characterize vilanterol pharmacokinetics using combined data from clinical trials in pediatric patients aged 5 to 11 years (n = 142). There was no relevant effect of age, weight, body mass index, sex, ethnicity, and race on vilanterol clearance. A cross-study comparison in pediatric patients with asthma showed that at steady-state, when combined with fluticasone furoate, vilanterol had

similar AUC values but lower C_{max} values compared to vilanterol administered alone. Vilanterol systemic exposure at steady state, in patients with asthma aged 5 to 11 years, was similar to those observed in adult and pediatric patients 12 years and older with asthma following repeat dosing of BREO ELLIPTA 100/25 mcg.

Racial or Ethnic Groups: Fluticasone Furoate: Systemic exposure [$AUC_{(0-24)}$] to inhaled fluticasone furoate 200 mcg was 27% to 49% higher in healthy subjects of Japanese, Korean, and Chinese heritage compared with White subjects. Similar differences were observed for patients with COPD or asthma (Figure 1). However, there is no evidence that this higher exposure to fluticasone furoate results in clinically relevant effects on urinary cortisol excretion or on efficacy in these racial groups.

Vilanterol: There was no effect of race on the pharmacokinetics of vilanterol in patients with COPD. In patients with asthma, vilanterol C_{max} is estimated to be higher (3-fold) and $AUC_{(0-24)}$ comparable for those patients from an Asian heritage compared with patients from a non-Asian heritage. However, the higher C_{max} values are similar to those seen in healthy subjects.

Patients with Hepatic Impairment: Fluticasone Furoate: Following repeat dosing of fluticasone furoate/vilanterol 200/25 mcg (100/12.5 mcg in the severe impairment group) for 7 days, there was an increase of 34%, 83%, and 75% in fluticasone furoate systemic exposure (AUC) in patients with mild, moderate, and severe hepatic impairment, respectively, compared with healthy subjects (Figure 1).

In patients with moderate hepatic impairment receiving fluticasone furoate/vilanterol 200/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% (90% CI: 11%, 51%) compared with healthy subjects. In patients with severe hepatic impairment receiving fluticasone furoate/vilanterol 100/12.5 mcg, mean serum cortisol (0 to 24 hours) was increased by 14% (90% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic disease should be closely monitored.

Vilanterol: Hepatic impairment had no effect on vilanterol systemic exposure [C_{max} and $AUC_{(0-24)}$ on Day 7] following repeat-dose administration of fluticasone furoate/vilanterol 200/25 mcg (100/12.5 mcg in the severe impairment group) for 7 days (Figure 1).

There were no additional clinically relevant effects of the fluticasone furoate/vilanterol combinations on heart rate or serum potassium in patients with mild or moderate hepatic impairment (vilanterol 25 mcg combination) or with severe hepatic impairment (vilanterol 12.5 mcg combination) compared with healthy subjects.

Patients with Renal Impairment: Fluticasone furoate systemic exposure was not increased and vilanterol systemic exposure [$AUC_{(0-24)}$] was 56% higher in patients with severe renal impairment compared with healthy subjects (Figure 1). There was no evidence of greater corticosteroid or beta-agonist class-related systemic effects (assessed by serum cortisol, heart

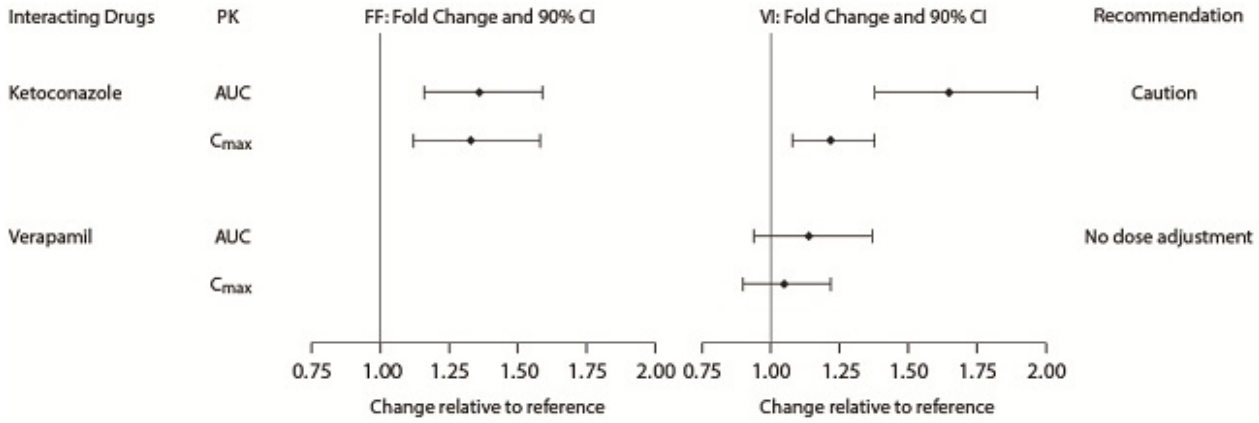
rate, and serum potassium) in patients with severe renal impairment compared with healthy subjects.

Drug Interaction Studies

There were no clinically relevant differences in the pharmacokinetics or pharmacodynamics of either fluticasone furoate or vilanterol when administered in combination compared with administration alone. The potential for fluticasone furoate and vilanterol to inhibit or induce metabolic enzymes and transporter systems is negligible at low inhalation doses.

Inhibitors of Cytochrome P450 3A4: The exposure (AUC) of fluticasone furoate and vilanterol were 36% and 65% higher, respectively, when coadministered with ketoconazole 400 mg compared with placebo (Figure 2). The increase in fluticasone furoate exposure was associated with a 27% reduction in weighted mean serum cortisol (0 to 24 hours). The increase in vilanterol exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate or blood potassium.

Figure 2. Impact of Coadministered Drugs[a] on the Pharmacokinetics (PK) of Fluticasone Furoate (FF) and Vilanterol (VI) Following Administration as Fluticasone Furoate/Vilanterol Combination or Vilanterol Coadministered with a Long-acting Muscarinic Antagonist



[a] Compared with placebo group.

Inhibitors of P-glycoprotein: Fluticasone furoate and vilanterol are both substrates of P-glycoprotein (P-gp). Coadministration of repeat-dose (240 mg once daily) verapamil (a moderate CYP3A4 inhibitor and a P-gp inhibitor) did not affect the vilanterol C_{max} or AUC in healthy subjects (Figure 2). Drug interaction trials with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

BREO ELLIPTA

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with BREO ELLIPTA; however, studies are available for the individual components, fluticasone furoate and vilanterol, as described below.

Fluticasone Furoate

Fluticasone furoate produced no treatment-related increases in the incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and 19 mcg/kg/day, respectively (both approximately 0.5 times the MRHDID of 200 mcg on a mcg/m^2 basis).

Fluticasone furoate did not induce gene mutation in bacteria or chromosomal damage in a mammalian cell mutation test in mouse lymphoma L5178Y cells in vitro. There was also no evidence of genotoxicity in the in vivo micronucleus test in rats.

No evidence of impairment of fertility was observed in male and female rats at inhaled fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 8 times, respectively, the MRHDID of 200 mcg for adults on an AUC basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhaled dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID on an AUC basis). No increase in tumors was seen at an inhaled dose of 615 mcg/kg/day (approximately 530 times the MRHDID on an AUC basis).

In a 2-year carcinogenicity study in rats, vilanterol caused statistically significant increases in mesovarian leiomyomas in females and shortening of the latency of pituitary tumors at inhaled doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID on an AUC basis).

These tumor findings in rodents are similar to those reported previously for other beta-adrenergic agonist drugs. The relevance of these findings to human use is unknown.

Vilanterol tested negative in the following genotoxicity assays: the in vitro Ames assay, in vivo rat bone marrow micronucleus assay, in vivo rat unscheduled DNA synthesis (UDS) assay, and in vitro Syrian hamster embryo (SHE) cell assay. Vilanterol tested equivocal in the in vitro mouse lymphoma assay.

No evidence of impairment of fertility was observed in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (both approximately 5,490 times the MRHDID based on AUC).

14 CLINICAL STUDIES

14.1 Chronic Obstructive Pulmonary Disease

Four trials evaluated the efficacy of BREO ELLIPTA on lung function (Trial 1, NCT01053988 and Trial 2, NCT01054885) and exacerbations (Trial 3, NCT01009463 and Trial 4, NCT01017952).

Lung Function: Trials 1 and 2 were 24-week, randomized, double-blind, placebo-controlled trials designed to evaluate the efficacy of BREO ELLIPTA on lung function in patients with COPD. In Trial 1, patients were randomized to BREO ELLIPTA 100/25 mcg, BREO ELLIPTA 200/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, and placebo. In Trial 2, patients were randomized to BREO ELLIPTA 100/25 mcg, fluticasone furoate/vilanterol 50/25 mcg, fluticasone furoate 100 mcg, vilanterol 25 mcg, and placebo. All treatments were administered as 1 inhalation once daily.

Of the 2,254 patients, 70% were male and 84% were White. They had a mean age of 62 years and an average smoking history of 44 pack years, with 54% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 14% to 87%), mean postbronchodilator FEV_1/FVC ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to 152%).

The co-primary efficacy variables in both trials were weighted mean FEV_1 (0 to 4 hours) postdose on Day 168 and change from baseline in trough FEV_1 on Day 169 (the mean of the FEV_1 values obtained 23 and 24 hours after the final dose on Day 168). The weighted mean comparison of the fluticasone furoate/vilanterol combination with fluticasone furoate was assessed to evaluate the contribution of vilanterol to BREO ELLIPTA. The trough FEV_1 comparison of the fluticasone furoate/vilanterol combination with vilanterol was assessed to evaluate the contribution of fluticasone furoate to BREO ELLIPTA.

BREO ELLIPTA 100/25 mcg demonstrated a larger increase in the weighted mean FEV_1 (0 to 4 hours) relative to placebo and fluticasone furoate 100 mcg at Day 168 (Table 6).

Table 6. Least Squares Mean Change from Baseline in Weighted Mean FEV_1 (0-4 h) and Trough FEV_1 at 6 Months

Treatment	N	Weighted Mean FEV_1 (0-4 h)[a] (mL) Difference from Placebo (95% CI)	Weighted Mean FEV_1 (0-4 h)[a] (mL) Difference from Fluticasone Furoate 100 mcg (95% CI)	Weighted Mean FEV_1 (0-4 h)[a] (mL) Difference from Fluticasone Furoate 200 mcg (95% CI)	Trough FEV_1[b] (mL) Difference from Placebo (95% CI)	Trough FEV_1[b] (mL) Difference from Vilanterol 25 mcg (95% CI)
Trial 1						
BREO ELLIPTA 100/25 mcg	204	214 (161, 266)	168 (116, 220)	—	144 (91, 197)	45 (-8, 97)
BREO ELLIPTA 200/25 mcg	205	209 (157, 261)	—	168 (117, 219)	131 (80, 183)	32 (-19, 83)
Trial 2						
BREO ELLIPTA 100/25 mcg	206	173 (123, 224)	120 (70, 170)	—	115 (60, 169)	48 (-6, 102)

FEV_1 = Forced Expiratory Volume in 1 second.

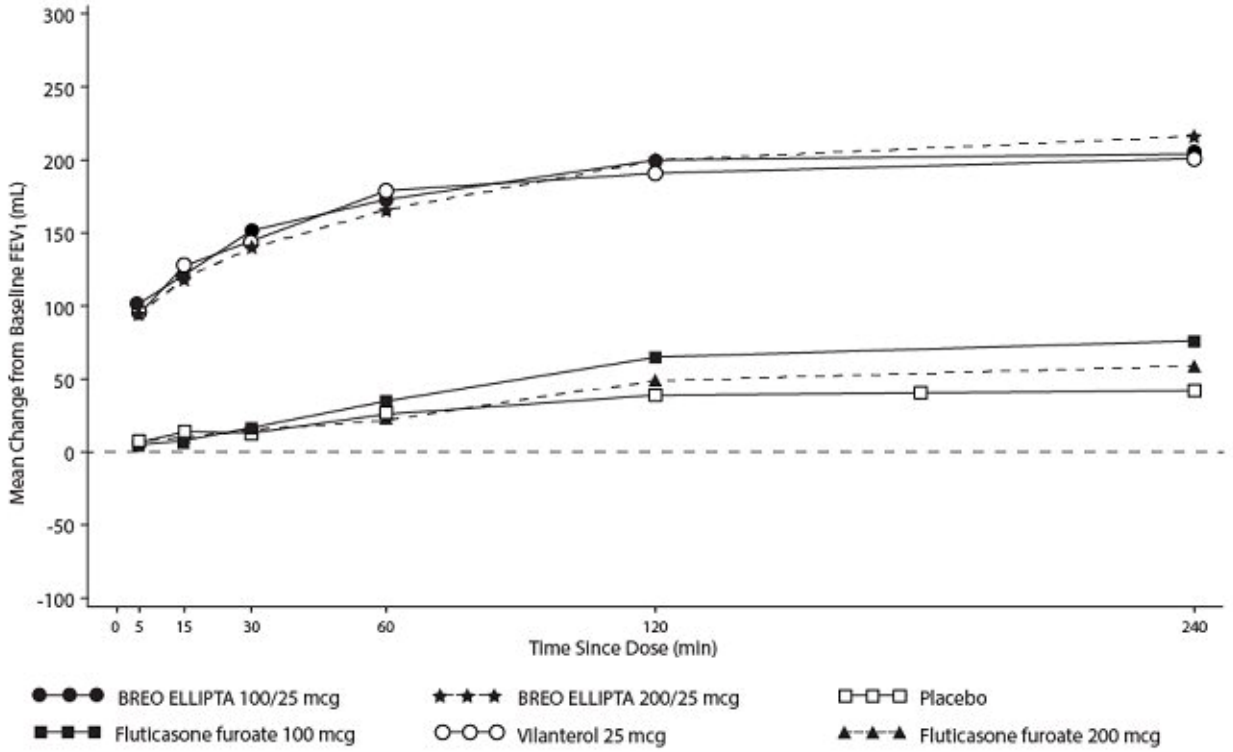
[a] At Day 168.

[b] At Day 169.

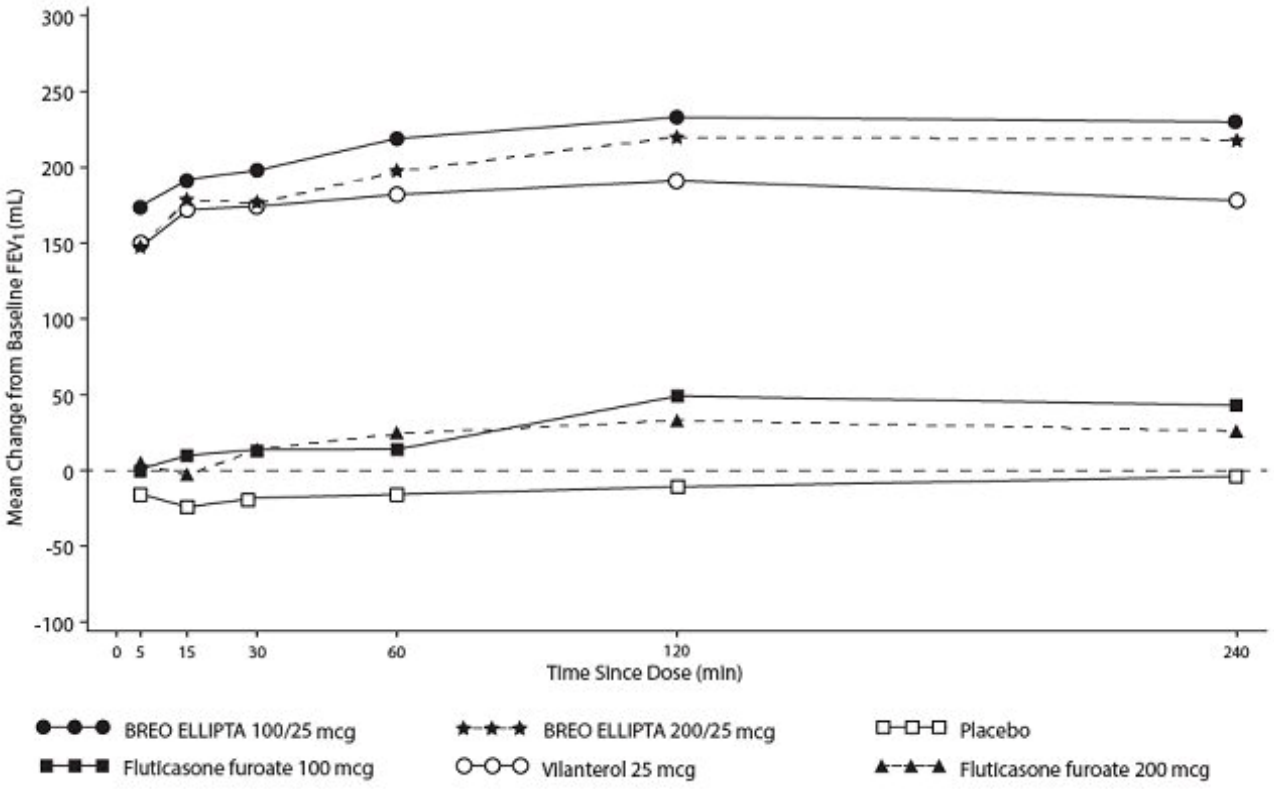
Serial spirometric evaluations were performed predose and up to 4 hours after dosing. Results from Trial 1 at Day 1 and Day 168 are shown in Figure 3. Similar results were seen in Trial 2 (not shown).

Figure 3. Raw Mean Change from Baseline in Postdose Serial FEV_1 (0-4 h) (mL) on Days 1 and 168

Day 1



Day 168



The second co-primary variable was change from baseline in trough FEV_1 following the final treatment day. At Day 169, both Trials 1 and 2 demonstrated significant increases in trough FEV_1 for all strengths of the fluticasone furoate/vilanterol combination compared with placebo (Table 7). The comparison of BREO ELLIPTA 100/25 mcg with vilanterol did not achieve statistical significance (Table 7).

Trials 1 and 2 evaluated FEV_1 as a secondary endpoint. Peak FEV_1 was defined as the maximum postdose FEV_1 recorded within 4 hours after the first dose of trial medicine on Day 1 (measurements recorded at 5, 15, and 30 minutes and 1, 2, and 4 hours). In both trials, differences in mean change from baseline in peak FEV_1 were observed for the groups receiving BREO ELLIPTA 100/25 mcg compared with placebo (152 and 139 mL, respectively). The median time to onset, defined as a 100-mL increase from baseline in FEV_1, was 16 minutes in patients receiving BREO ELLIPTA 100/25 mcg.

Exacerbations: Trials 3 and 4 were randomized, double-blind, 52-week trials designed to evaluate the effect of BREO ELLIPTA on the rate of moderate and severe COPD exacerbations. All patients were treated with fluticasone propionate/salmeterol 250/50 mcg twice daily during a 4-week run-in period prior to being randomly assigned to 1 of the following treatment groups: BREO ELLIPTA 100/25 mcg, BREO ELLIPTA 200/25 mcg, fluticasone furoate/vilanterol 50/25 mcg, or vilanterol 25 mcg.

The primary efficacy variable in both trials was the annual rate of moderate/severe exacerbations. The comparison of the fluticasone furoate/vilanterol combination with vilanterol was assessed to evaluate the contribution of fluticasone furoate to BREO ELLIPTA. In these 2 trials, exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered to be of moderate severity if treatment with systemic corticosteroids and/or antibiotics was required and were considered to be severe if hospitalization was required.

Trials 3 and 4 included 3,255 patients, of which 57% were male and 85% were White. They had a mean age of 64 years and an average smoking history of 46 pack years, with 44% identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 45% (range: 12% to 91%), and mean postbronchodilator FEV_1/FVC ratio was 46% (range: 17% to 81%), indicating that the patient population had moderate to very severely impaired airflow obstruction. The mean percent reversibility was 15% (range: -65% to 313%).

Patients treated with BREO ELLIPTA 100/25 mcg had a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol in both trials (Table 7).

Table 7. Moderate and Severe Chronic Obstructive Pulmonary Disease Exacerbations

Treatment	n	Mean Annual Rate (exacerbations/year)	Ratio vs. Vilanterol	95% CI
Trial 3				
BREO ELLIPTA 100/25 mcg	403	0.90	0.79	0.64, 0.97
BREO ELLIPTA 200/25 mcg	409	0.79	0.69	0.56, 0.85
Fluticasone furoate/vilanterol 50/25 mcg	412	0.92	0.81	0.66, 0.99
Vilanterol 25 mcg	409	1.14	—	—
Trial 4				
BREO ELLIPTA 100/25 mcg	403	0.70	0.66	0.54, 0.81
BREO ELLIPTA 200/25 mcg	402	0.90	0.85	0.70, 1.04
Fluticasone furoate/vilanterol 50/25 mcg	408	0.92	0.87	0.72, 1.06
Vilanterol 25 mcg	409	1.05	—	—

Comparator Trials

Three 12-week, randomized, double-blind, double-dummy trials were conducted with BREO ELLIPTA 100/25 mcg once daily versus fluticasone propionate/salmeterol 250/50 mcg twice daily to evaluate the efficacy of serial lung function of BREO ELLIPTA in patients with COPD.

The primary endpoint of each trial was change from baseline in weighted mean FEV_1 (0 to 24 hours) on Day 84. Of the 519 patients in Trial 5 (NCT01323634), 64% were male and 97% were White; mean age was 61 years; average smoking history was 40 pack years, with 55% identified as current smokers. At screening in the treatment group using BREO ELLIPTA 100/25 mcg, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 19% to 70%), the mean (SD) FEV_1/FVC ratio was 0.51 (0.11), and the mean percent reversibility was 11% (range: -12% to 83%). At screening in the treatment group using fluticasone propionate/salmeterol 250/50 mcg, the mean postbronchodilator percent predicted FEV_1 was 47% (range: 14% to 71%), the mean (SD) FEV_1/FVC ratio was 0.49 (0.10), and the mean percent reversibility was 11% (range: -13% to 50%).

Of the 511 patients in Trial 6 (NCT01323621), 68% were male and 94% were White; mean age was 62 years; average smoking history was 35 pack years, with 52% identified as current smokers. At screening in the treatment group using BREO ELLIPTA 100/25 mcg, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 18% to 70%), the mean (SD) FEV_1/FVC ratio was 0.51 (0.10), and the mean percent reversibility was 12% (range: -56% to 77%). At screening in the treatment group using fluticasone propionate/salmeterol 250/50 mcg, the mean postbronchodilator percent predicted FEV_1 was 49% (range: 15% to 70%), the mean (SD) FEV_1/FVC ratio was 0.50 (0.10), and the mean percent reversibility was 12% (range: -66% to 72%).

Of the 828 patients in Trial 7 (NCT01706328), 72% were male and 98% were White; mean age was 61 years; average smoking history was 38 pack years, with 60% identified as current smokers. At screening in the treatment group using BREO ELLIPTA 100/25 mcg, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 18% to 70%), the mean (SD) FEV_1/FVC ratio was 0.52 (0.10), and the mean percent reversibility was 12% (range: -26% to 84%). At screening in the treatment group using fluticasone propionate/salmeterol 250/50 mcg, the mean postbronchodilator percent predicted FEV_1 was 48% (range: 16% to 70%), the mean (SD) FEV_1/FVC ratio was 0.51 (0.10), and the mean percent reversibility was 12% (range: -15% to 67%).

In Trial 5, the mean (SE) change from baseline in weighted mean FEV_1 (0 to 24 hours) with BREO ELLIPTA 100/25 mcg was 174 (15) mL compared with 94 (16) mL with fluticasone propionate/salmeterol 250/50 mcg (treatment difference 80 mL; 95% CI: 37, 124; $P<0.001$). In Trials 6 and 7, the mean (SE) change from baseline in weighted mean FEV_1 (0 to 24 hours) with BREO ELLIPTA 100/25 mcg was 142 (18) mL and 168 (12) mL, respectively, compared with 114 (18) mL and 142 (12) mL, respectively, for fluticasone propionate/salmeterol 250/50 mcg (Trial 6 treatment difference 29 mL; 95% CI: -22, 80; $P = 0.267$; Trial 7 treatment difference 25 mL; 95% CI: -8, 59; $P = 0.137$).

Mortality Trial

A randomized, double-blind, multicenter, multinational trial (NCT01313676) prospectively evaluated the efficacy of BREO ELLIPTA 100/25 mcg compared with placebo on survival. The trial was event-driven and patients were followed until a sufficient number of deaths occurred. In this trial, 16,568 patients aged 40 to 80 years received BREO ELLIPTA 100/25 mcg (n = 4,140), fluticasone furoate 100 mcg (n = 4,157), vilanterol 25 mcg (n = 4,140), or placebo (n = 4,131). Patients were treated for up to 4 years, with a median treatment duration of 1.5 years. Median duration of follow-up for the endpoint of survival was 1.8 years for all treatment groups. All patients had COPD with moderate airflow limitation (≥50% and ≤70% predicted FEV_1) and either had a history of, or were at risk of, cardiovascular disease. The primary endpoint was all-cause mortality. Secondary efficacy endpoints included the rate of decline in FEV_1, annual rate of moderate/severe COPD exacerbations, and health-related quality of life as measured by the St. George's Respiratory Questionnaire for COPD patients (SGRQ-C).

Survival: Survival with BREO ELLIPTA 100/25 mcg was not significantly improved compared with placebo (hazard ratio 0.88; 95% CI: 0.74, 1.04). Mortality per 100 patient-years was 3.1 for BREO ELLIPTA 100/25 mcg, 3.5 for placebo, 3.2 for fluticasone furoate, and 3.4 for vilanterol.

Lung Function: A reduction of 8 mL/year was estimated on-treatment for BREO ELLIPTA 100/25 mcg compared with placebo in the rate of lung function decline as measured by FEV_1 (95% CI: 1, 15).

Exacerbations: Treatment with BREO ELLIPTA 100/25 mcg reduced the on-treatment annual rate of moderate/severe exacerbations by 29% compared with placebo (95% CI: 22, 35). Treatment with BREO ELLIPTA 100/25 mcg reduced the annual rate of moderate/severe exacerbations by 19% compared with fluticasone furoate (95% CI: 12, 26) and by 21% compared with vilanterol (95% CI: 14, 28). The on-treatment annual rate of moderate/severe exacerbations was 0.25 for BREO ELLIPTA 100/25 mcg, 0.35 for placebo, 0.31 for fluticasone furoate, and 0.31 for vilanterol.

Treatment with BREO ELLIPTA 100/25 mcg reduced the on-treatment annual rate of severe exacerbations (i.e., requiring hospitalization) by 27% compared with placebo (95% CI: 13, 39). Treatment with BREO ELLIPTA 100/25 mcg reduced the on-treatment annual rate of exacerbations requiring hospitalization by 11% compared with fluticasone furoate (95% CI: -6, 25) and by 9% compared with vilanterol (95% CI: -8, 24).

Health-Related Quality of Life: The St. George's Respiratory Questionnaire (SGRQ) is a disease-specific patient-reported instrument that measures symptoms, activities, and impact on daily life. The SGRQ-C, a shorter version derived from the original SGRQ, was used in this trial. Results were transformed to the SGRQ for reporting purposes. In a subset of 4,443 patients, the on-treatment SGRQ responder rates at 1 year (defined as a change in score of 4 or more as threshold) were 49% for BREO ELLIPTA 100/25 mcg, 47% for placebo, 48% for fluticasone

furoate, and 48% for vilanterol (odds ratio 1.18; 95% CI: 0.97, 1.44 for BREO ELLIPTA 100/25 mcg compared with placebo).

14.2 Asthma

Adult Patients

The efficacy of BREO ELLIPTA for the maintenance treatment of asthma was based on data from 4 randomized, double-blind, parallel-group clinical trials (Trial 8 [NCT01165138], Trial 9 [NCT01686633], Trial 10 [NCT01134042] and Trial 12 [NCT01086384]). While these 4 trials enrolled pediatric patients 12 to 17 years of age, these trials only support efficacy in adults *[see Use in Specific Populations (8.4)]*. In addition, patients in these trials were treated with BREO ELLIPTA 200/25 mcg once daily by oral inhalation, which is not the approved recommended dosage for pediatric patients 12 years of age and older *[see Dosage and Administration (2.3)]*. Trials 8, 9, and 10 were designed to evaluate the safety and efficacy of BREO ELLIPTA given once daily in patients who were not controlled on their current treatments of ICS or combination therapy consisting of an ICS plus a LABA. Trial 12 (24- to 76-week exacerbation trial) was designed to demonstrate that treatment with BREO ELLIPTA 100/25 mcg significantly decreased the risk of asthma exacerbations as measured by time to first asthma exacerbation when compared with fluticasone furoate 100 mcg. This trial enrolled patients who had 1 or more asthma exacerbations in the year prior to trial entry. The demographics of these 4 trials and the comparator trial (Trial 13, NCT01147848) are provided in Table 8.

Table 8. Demography of Asthma Trials 8, 9, 10, 12, and 13

Parameter	Trial 8 n = 609	Trial 9 n = 1,039	Trial 10 n = 586	Trial 12 n = 2,019	Trial 13 n = 806
Mean age (years) (range) for all patients	40 (12, 84)	46 (12, 82)	46 (12, 76)	42 (12, 82)	43 (12, 80)
Mean age (years) (range) for adult patients	44 (18, 84)	48 (18, 82)	47 (18, 76)	46 (18, 82)	46 (18, 80)
Female (%)	58	60	59	67	61
White (%)	84	88	84	73	59
Duration of asthma (years)	12	18	16	16	21
Never smoked[a] (%)	N/A	84	N/A	86	81
Predose FEV_1 (L) at baseline	2.32	1.97	2.15	2.20	2.03
Mean percent predicted FEV_1 at baseline (%)	70	62	67	72	68
% Reversibility	29	30	29	24	28
Absolute reversibility (mL)	614	563	571	500	512

N/A = Data not collected.

[a] Trials did not include current smokers; past smokers had fewer than 10 packs per year history.

Trials 8, 9, and 10 were 12- or 24-week trials that evaluated the efficacy of BREO ELLIPTA on lung function in patients with asthma. In Trial 8, patients were randomized to BREO ELLIPTA 100/25 mcg, fluticasone furoate 100 mcg, or placebo. In Trial 9, patients were randomized to BREO ELLIPTA 100/25 mcg, BREO ELLIPTA 200/25 mcg, or fluticasone furoate 100 mcg. In Trial 10, patients were randomized to BREO ELLIPTA 200/25 mcg, fluticasone furoate 200 mcg, or fluticasone propionate 500 mcg. All inhalations were administered once daily, with the exception of fluticasone propionate, which was administered twice daily. Patients receiving an ICS or an ICS plus a LABA (doses of ICS varied by trial and asthma severity) entered a 4-week run-in period during which LABA treatment was stopped. Patients reporting symptoms and/or rescue beta$_2$-agonist medication use during the run-in period were continued in the trial.

In Trials 8 and 10, change from baseline in weighted mean FEV_1 (0 to 24 hours) and change from baseline in trough FEV_1 at approximately 24 hours after the last dose at study endpoint (12 and 24 weeks, respectively) were co-primary efficacy endpoints. In Trial 9, change from baseline in weighted mean FEV_1 (0 to 24 hours) at Week 12 was the primary efficacy endpoint; change from baseline in trough FEV_1 at approximately 24 hours after the last dose at Week 12 was a secondary endpoint. Table 9 provides the change from baseline in weighted mean FEV_1 in mL (0 to 24 hours) and trough FEV_1 in mL at study endpoint. Weighted mean FEV_1 (0 to 24 hours) was derived from serial measurements taken within 30 minutes prior to dosing and post-dose assessments at 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours after the final dose. Other secondary endpoints included change from baseline in percentage of rescue-free 24-hour periods and percentage of symptom-free 24-hour periods over the treatment period.

Table 9. Change from Baseline in Weighted Mean FEV_1 (0-24 h) (mL) and Trough FEV_1 (mL) at Study Endpoint (Trials 8, 9, and 10)[a]

Study (Duration) Background Treatment Treatment	n	Weighted Mean FEV_1 (0-24 h) (mL) Difference from Placebo (95% CI)	Fluticasone Furoate 100 mcg (95% CI)	Fluticasone Furoate 200 mcg (95% CI)
Trial 8 (12 Weeks) Low- to mid-dose ICS or low-dose ICS + LABA				
BREO ELLIPTA 100/25 mcg	108	302 (178, 426)	116 (-5, 236)	—
Trial 9 (12 Weeks) Mid- to high-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 100/25 mcg	312	—	108 (45, 171)	—
Trial 10 (24 Weeks) High-dose ICS or mid-dose ICS + LABA				

BREO ELLIPTA 200/25 mcg	89	—	—	136 (1, 270)
Study (Duration) Background Treatment		**Trough FEV_1 (mL) Difference from**		
Treatment	**n**	**Placebo (95% CI)**	**Fluticasone Furoate 100 mcg (95% CI)**	**Fluticasone Furoate 200 mcg (95% CI)**
Trial 8 (12 Weeks) Low- to mid-dose ICS or low-dose ICS + LABA				
BREO ELLIPTA 100/25 mcg	200	172 (87, 258)	36 (-48, 120)	—
Trial 9 (12 Weeks) Mid- to high-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 100/25 mcg	334	—	77 (16, 138)	—
Trial 10 (24 Weeks) High-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 200/25 mcg	187	—	—	193 (108, 277)

FEV_1 = Forced Expiratory Volume in 1 second, ICS = inhaled corticosteroid, LABA = long-acting beta$_2$-adrenergic agonist.

[a] Although these trials included pediatric patients 12 to 17 years of age, they only support the efficacy in adult patients.

In Trial 8, weighted mean FEV_1 (0 to 24 hours) was assessed in a subset of patients (n = 309). At Week 12, change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for BREO ELLIPTA 100/25 mcg compared with placebo (302 mL; 95% CI: 178, 426; $P<0.001$) (Table 9); change from baseline in weighted mean FEV_1 (0 to 24 hours) for BREO ELLIPTA 100/25 mcg was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (116 mL; 95% CI: -5, 236). At Week 12, change from baseline in trough FEV_1 was significantly greater for BREO ELLIPTA 100/25 mcg compared with placebo (172 mL; 95% CI: 87, 258; $P<0.001$) (Table 9); change from baseline in trough FEV_1 for BREO ELLIPTA 100/25 mcg was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (36 mL; 95% CI: -48, 120).

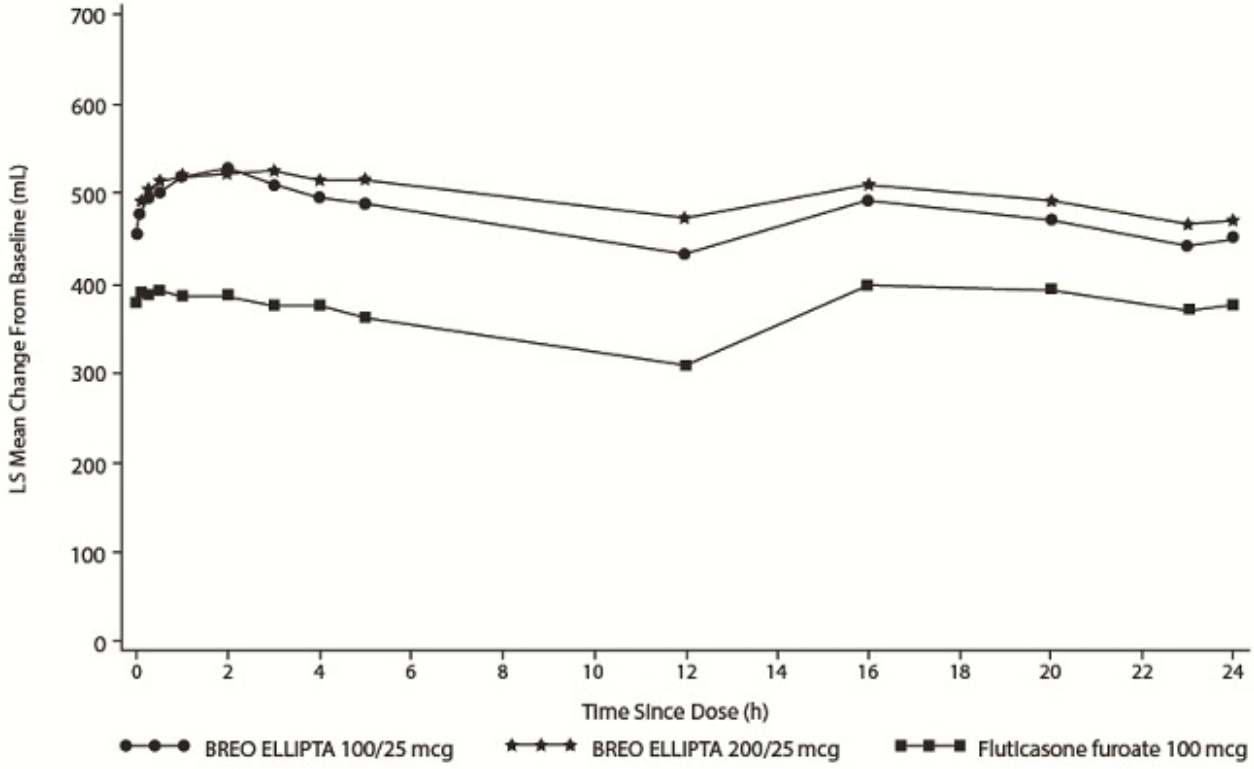
In Trial 9, the change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for BREO ELLIPTA 100/25 mcg compared with fluticasone furoate 100 mcg (108 mL; 95% CI: 45, 171; $P<0.001$) at Week 12 (Table 9). In a descriptive analysis, the change from baseline in weighted mean FEV_1 (0 to 24 hours) for BREO ELLIPTA 200/25 mcg was numerically greater than BREO ELLIPTA 100/25 mcg (24 mL; 95% CI: -37, 86) at Week 12. The change from baseline in trough FEV_1 was significantly greater for BREO ELLIPTA

100/25 mcg compared with fluticasone furoate 100 mcg (77 mL, 95% CI: 16, 138; $P = 0.014$) at Week 12 (Table 9). In a descriptive analysis, the change from baseline in trough FEV_1 for BREO ELLIPTA 200/25 mcg was numerically greater than BREO ELLIPTA 100/25 mcg (16 mL; 95% CI: -46, 77) at Week 12.

In Trial 10, the change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for BREO ELLIPTA 200/25 mcg compared with fluticasone furoate 200 mcg (136 mL; 95% CI: 1, 270; $P = 0.048$) at Week 24 (Table 0). The change from baseline in trough FEV_1 was significantly greater for BREO ELLIPTA 200/25 mcg compared with fluticasone furoate 200 mcg (193 mL, 95% CI: 108, 277; $P<0.001$) at Week 24.

Lung function improvements were demonstrated through weighted mean FEV_1 (0 to 24 hours) over the 24-hour period following the final dose of BREO ELLIPTA in Trials 9 and 10. Serial FEV_1 measurements were taken within 30 minutes prior to dosing and postdose assessments at 5, 15, and 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23, and 24 hours in Trials 1, 2, and 3. A representative figure is shown from Trial 9 in Figure 4.

Figure 4. Least Squares (LS) Mean Change from Baseline in Individual Serial FEV_1 (mL) Assessments over 24 Hours after 12 Weeks of Treatment (Trial 9)[a]



[a] Although these trials included pediatric patients 12 to 17 years of age, the data only support the efficacy in adult patients.

Patients receiving BREO ELLIPTA 100/25 mcg (Trial 9) or BREO ELLIPTA 200/25 mcg (Trial 10) had significantly greater improvements from baseline in percentage of 24-hour periods

without need of beta$_2$-agonist rescue medication use and percentage of 24-hour periods without asthma symptoms compared with patients receiving fluticasone furoate 100 mcg or fluticasone furoate 200 mcg, respectively. In a descriptive analysis (Trial 9), patients receiving BREO ELLIPTA 200/25 mcg had numerical improvements from baseline in percentage of 24-hour periods without need of beta$_2$-agonist rescue medication use and percentage of 24-hour periods without asthma symptoms compared with patients receiving BREO ELLIPTA 100/25 mcg.

Trial 12 was a 24- to 76-week event-driven exacerbation trial that evaluated whether BREO ELLIPTA 100/25 mcg significantly decreased the risk of asthma exacerbations as measured by time to first asthma exacerbation when compared with fluticasone furoate 100 mcg in patients with asthma. Patients receiving low- to high-dose ICS (fluticasone propionate 100 mcg to 500 mcg twice daily or equivalent) or low- to mid-dose ICS plus a LABA (fluticasone propionate/salmeterol 100/50 mcg to 250/50 mcg twice daily or equivalent) and a history of 1 or more asthma exacerbations that required treatment with oral/systemic corticosteroid or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to trial entry, entered a 2-week run-in period during which LABA treatment was stopped. Patients reporting symptoms and/or rescue beta$_2$-agonist medication use during the run-in period were continued in the trial.

The primary endpoint was time to first asthma exacerbation. Asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroid for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroid. Rate of asthma exacerbation was a secondary endpoint. The hazard ratio from the Cox Model for the analysis of time to first asthma exacerbation for BREO ELLIPTA 100/25 mcg compared with fluticasone furoate 100 mcg was 0.795 (95% CI: 0.642, 0.985). This represents a 20% reduction in the risk of experiencing an asthma exacerbation for patients treated with BREO ELLIPTA 100/25 mcg compared with fluticasone furoate 100 mcg (P = 0.036). Mean yearly rates of asthma exacerbations of 0.14 and 0.19 in patients treated with BREO ELLIPTA 100/25 mcg compared with fluticasone furoate 100 mcg, respectively, were observed (25% reduction in rate; 95% CI: 5%, 40%).

Comparator Trial

Trial 13 was a 24-week trial that compared the efficacy of BREO ELLIPTA 100/25 mcg once daily with fluticasone propionate/salmeterol 250/50 mcg twice daily (N = 806). Patients receiving mid-dose ICS (fluticasone propionate 250 mcg twice daily or equivalent) entered a 4-week run-in period during which all patients received fluticasone propionate 250 mcg twice daily. The primary endpoint was change from baseline in weighted mean FEV$_1$ (0 to 24 hours) at Week 24.

The mean change (SE) from baseline in weighted mean FEV$_1$ (0 to 24 hours) for BREO ELLIPTA 100/25 mcg was 341 (18.4) mL compared with 377 (18.5) mL for fluticasone propionate/salmeterol 250/50 mcg (treatment difference -37 mL; 95% CI: -88, 15; P = 0.162).

Pediatric Patients Aged 5 to 17 Years

The efficacy of BREO ELLIPTA for the maintenance treatment of asthma in pediatric patients aged 5 to 17 years of age was based on Trial 14 (NCT03248128), a 24-week, randomized, double-blind, stratified, parallel-group clinical trial. This trial evaluated the efficacy of BREO ELLIPTA compared with fluticasone furoate in 902 pediatric patients with asthma aged 5 to 17 years who were uncontrolled on their current ICS treatment. All inhalations were administered once daily in the morning. At trial entry patients had at least a 6-month history of asthma and had been receiving stable asthma therapy for at least 4 weeks prior to screening. Patients had to have a pre-bronchodilator FEV_1 >50% to ≤100% of predicted normal and demonstrate a ≥12% reversibility of FEV_1 within 15 to 40 minutes following 2 to 4 inhalations of albuterol inhalation aerosol (or 1 nebulized treatment with albuterol solution). Exclusion criteria included a history of life-threatening asthma or any asthma exacerbation requiring the use of oral corticosteroids, systemic or depot corticosteroids, emergency department visit, or hospitalization within 6 weeks, 3 months, 3 months, or 6 months of screening, respectively.

Patients entered a 4-week open-label run-in period during which all patients received fluticasone propionate 100 mcg twice daily. Patients reporting symptoms and/or rescue $beta_2$-agonist medication use during the last week of the run-in period were continued in the trial and were stratified by age. Pediatric patients aged 12 to 17 years (n = 229) were randomized 1:1 to BREO ELLIPTA 100/25 mcg once daily (n = 117) or fluticasone furoate 100 mcg once daily (n = 112). Pediatric patients aged 5 to 11 years (n = 673) were randomized 1:1 to BREO ELLIPTA 50/25 mcg once daily (n = 337) or fluticasone furoate 50 mcg once daily (n = 336). The primary endpoint was weighted mean FEV_1 (0 to 4 hours) at Week 12. Of the 902 patients, the mean age was 10.0 years, 61% were male, and 73% were White, 8% African American, 6% American Indian or Alaska Native, 6% Asian, and 7% Other. Lung function improvements based on the primary endpoint of weighted mean FEV_1 (0 to 4 hours) are presented in Table 10.

Table 10. Weighted Mean FEV_1 (0-4 h) (mL) at Week 12 in Patients Aged 5 to 17 Years (Intent to Treat Population)

Primary Endpoint	Fluticasone Furoate[a] (N = 448)	BREO ELLIPTA[b] (N = 454)
Weighted Mean FEV_1 (0-4 h) (mL)	n = 397	n = 394
LS mean	1999	2081
LS mean change (SE)	323 (16.4)	406 (16.5)
Difference vs fluticasone furoate (95% CI)		83 (37, 129)

FEV_1 = Forced Expiratory Volume in 1 second, LS = Least squares, SE = standard error.
[a]The dose of fluticasone furoate was 100 mcg once daily for pediatric patients aged 12 to 17 years and 50 mcg once daily for pediatric patients aged 5 to 11 years.

[b]The dose of BREO ELLIPTA was 100/25 mcg once daily for pediatric patients aged 12 to 17 years and 50/25 mcg once daily for pediatric patients aged 5 to 11 years.

Difference in LS mean change from baseline at Week 12 for BREO ELLIPTA 100/25 mcg compared with fluticasone furoate 100 mcg was 106 mL (95% CI: -8, 220) in pediatric patients 12 to 17 years of age, and difference in LS mean change from baseline at Week 12 for BREO ELLIPTA 50/25 mcg compared with fluticasone furoate 50 mcg was 73 mL (95% CI:28,118) in pediatric patients 5 to 11 years of age.

16 HOW SUPPLIED/STORAGE AND HANDLING

BREO ELLIPTA is supplied as a disposable light grey and pale blue plastic inhaler containing 2 foil strips, each with 30 blisters (or 14 blisters for the institutional pack).

One strip contains fluticasone furoate (50, 100 or 200 mcg per blister), and the other strip contains vilanterol (25 mcg per blister).

A blister from each strip is used to create 1 dose. The inhaler is packaged within a moisture-protective foil tray with a desiccant and a peelable lid in the following packs:

NDC 0173-0916-10	BREO ELLIPTA 50/25 mcg	30 inhalations (60 blisters)
NDC 0173-0859-10	BREO ELLIPTA 100/25 mcg	30 inhalations (60 blisters)
NDC 0173-0859-14	BREO ELLIPTA 100/25 mcg	14 inhalations (28 blisters), institutional pack
NDC 0173-0882-10	BREO ELLIPTA 200/25 mcg	30 inhalations (60 blisters)
NDC 0173-0882-14	BREO ELLIPTA 200/25 mcg	14 inhalations (28 blisters), institutional pack

Store at room temperature between 68°F and 77°F (20°C and 25°C); excursions permitted from 59°F to 86°F (15°C to 30°C) [See USP Controlled Room Temperature]. Store in a dry place away from direct heat or sunlight. Keep out of reach of children.

BREO ELLIPTA should be stored inside the unopened moisture-protective foil tray and only removed from the tray immediately before initial use. Discard BREO ELLIPTA 6 weeks after opening the foil tray or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable. Do not attempt to take the inhaler apart.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Serious Asthma-Related Events

Inform patients with asthma that LABA when used alone increases the risk of asthma-related hospitalization or asthma-related death. Available data show that when ICS and LABA are used

together, such as with BREO ELLIPTA, there is not a significant increase in the risk of these events. *[See Warnings and Precautions (5.1).]*

Not for Acute Symptoms

Inform patients that BREO ELLIPTA is not meant to relieve acute symptoms of COPD or asthma and extra doses should not be used for that purpose. Advise patients to treat acute symptoms with an inhaled, short-acting beta$_2$-agonist such as albuterol. Provide patients with such medication and instruct them in how it should be used.

Instruct patients to seek medical attention immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Tell patients they should not stop therapy with BREO ELLIPTA without physician/provider guidance since symptoms may recur after discontinuation. *[See Warnings and Precautions (5.2).]*

Do Not Use Additional Long-acting Beta$_2$-agonists

Instruct patients not to use other LABA for COPD and asthma. *[See Warnings and Precautions (5.3).]*

Oropharyngeal Candidiasis

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, treat it with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with BREO ELLIPTA, but at times therapy with BREO ELLIPTA may need to be temporarily interrupted under close medical supervision. Advise patients to rinse the mouth with water without swallowing after inhalation to help reduce the risk of thrush. *[See Warnings and Precautions (5.4).]*

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia. *[See Warnings and Precautions (5.5).]*

Immunosuppression and Risk of Infections

Warn patients who are on immunosuppressant doses of corticosteroids to avoid exposure to chickenpox or measles and, if exposed, to consult their physicians without delay. Inform patients of potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. *[See Warnings and Precautions (5.6).]*

Hypercorticism and Adrenal Suppression

Advise patients that BREO ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, inform patients that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to BREO ELLIPTA. *[See Warnings and Precautions (5.8).]*

Paradoxical Bronchospasm

As with other inhaled medicines, BREO ELLIPTA can cause paradoxical bronchospasm. If paradoxical bronchospasm occurs, instruct patients to discontinue BREO ELLIPTA and contact their healthcare provider right away. *[See Warnings and Precautions (5.10).]*

Hypersensitivity Reactions, including Anaphylaxis

Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash, urticaria) may occur after administration of BREO ELLIPTA. Instruct patients to discontinue BREO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of other powder medications containing lactose; therefore, patients with severe milk protein allergy should not use BREO ELLIPTA. *[See Warnings and Precautions (5.11).]*

Reduction in Bone Mineral Density

Advise patients who are at an increased risk for decreased BMD that the use of corticosteroids may pose an additional risk. *[See Warnings and Precautions (5.13).]*

Reduced Growth Velocity

Inform patients that orally inhaled corticosteroids, including fluticasone furoate, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children taking corticosteroids by any route. *[See Warnings and Precautions (5.14).]*

Glaucoma and Cataracts

Advise patients that long-term use of ICS may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations. *[See Warnings and Precautions (5.15).]*

Risks Associated with Beta-agonist Therapy

Inform patients of adverse effects associated with beta$_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness. Instruct patients to consult a healthcare practitioner immediately should any of these signs and symptoms develop. *[See Warnings and Precautions (5.12).]*

BREO ELLIPTA was developed in collaboration with Innoviva.

INNOVIVA

GSK

GlaxoSmithKline
Durham, NC 27701

BRE:xxPI

PATIENT INFORMATION

BREO ELLIPTA (BRE-oh e-LIP-ta)
(fluticasone furoate and vilanterol inhalation powder)
for oral inhalation use

What is BREO ELLIPTA?

- BREO ELLIPTA combines 2 medicines in 1 inhaler, an inhaled corticosteroid (ICS) medicine (fluticasone furoate) and a long-acting beta$_2$-adrenergic agonist (LABA) medicine (vilanterol).
  - ICS medicines such as fluticasone furoate help to decrease inflammation in the lungs. Inflammation in the lungs can lead to breathing problems.
  - LABA medicines such as vilanterol help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe.
- **BREO ELLIPTA is not used to relieve sudden breathing problems** and will not replace a rescue inhaler.
- BREO ELLIPTA is a prescription medicine used long term (chronic) to treat people with:

  Chronic Obstructive Pulmonary Disease (COPD):
  - BREO ELLIPTA is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both.
  - BREO ELLIPTA is used to improve symptoms of COPD for better breathing and to reduce the number of flare-ups (the worsening of your COPD symptoms for several days).

  Asthma:
  - BREO ELLIPTA is a prescription medicine used to prevent and control symptoms of asthma for better breathing and to prevent symptoms such as wheezing.
  - BREO ELLIPTA contains vilanterol. LABA medicines such as vilanterol when used alone increase the risk of hospitalizations and death from asthma problems. BREO ELLIPTA contains an ICS and a LABA. When an ICS and LABA are used together, there is **not** a significant increased risk in hospitalizations and death from asthma problems.

It is not known if BREO ELLIPTA is safe and effective in children younger than 5 years of age.

Do not use BREO ELLIPTA:

- to treat sudden, severe symptoms of COPD or asthma.
- if you have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.
- if you are allergic to fluticasone furoate, vilanterol, or any of the ingredients in BREO ELLIPTA. See the end of this Patient Information for a complete list of ingredients in BREO ELLIPTA.

Before using BREO ELLIPTA, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes or have been told you have high blood sugar.
- have liver problems.
- have weak bones (osteoporosis).

- have an immune system problem.
- have eye problems such as glaucoma, increased pressure in your eye, cataracts, or other changes in vision.
- are allergic to milk proteins.
- have any type of viral, bacterial, fungal, or parasitic infection.
- are exposed to chickenpox or measles.
- are pregnant or plan to become pregnant. It is not known if BREO ELLIPTA may harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if the medicines in BREO ELLIPTA pass into your breast milk and if they can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. BREO ELLIPTA and certain other medicines may interact with each other. This may cause serious side effects. Especially tell your healthcare provider if you take

- other LABA (including salmeterol, formoterol, arformoterol, olodaterol, and indacaterol)
- antifungal or anti-HIV medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use BREO ELLIPTA?

Read the step-by-step instructions for using BREO ELLIPTA at the end of this Patient Information.

- **Do not** use BREO ELLIPTA unless your healthcare provider has taught you how to use the inhaler and you understand how to use it correctly.
- BREO ELLIPTA comes in 3 different strengths. Your healthcare provider prescribed the strength that is best for you.
- Use BREO ELLIPTA exactly as your healthcare provider tells you to use it. **Do not** use BREO ELLIPTA more often than prescribed.
- Children may need help to use BREO ELLIPTA.
- Use 1 inhalation of BREO ELLIPTA 1 time each day. Use BREO ELLIPTA at the same time each day.
- If you miss a dose of BREO ELLIPTA, take it as soon as you remember. Do not take more than 1 inhalation per day. Take your next dose at your usual time. Do not take 2 doses at 1 time.
- If you take too much BREO ELLIPTA, call your healthcare provider or go to the nearest hospital emergency room right away if you have any unusual symptoms, such as worsening shortness of breath, chest pain, increased heart rate, or shakiness.
- **Do not use other medicines that contain a LABA for any reason.** Ask your healthcare provider or pharmacist if any of your other medicines are LABA medicines.
- **Do not** stop using BREO ELLIPTA unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **BREO ELLIPTA does not relieve sudden symptoms of COPD or asthma and you should not take extra doses of BREO ELLIPTA to relieve these sudden symptoms.** Always have a rescue inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler, call your healthcare provider to have one prescribed for you.
- Call your healthcare provider or get medical care right away if:
  - your breathing problems get worse.
  - you need to use your rescue inhaler more often than usual.
  - your rescue inhaler does not work as well to relieve your symptoms.
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.

What are the possible side effects of BREO ELLIPTA?

BREO ELLIPTA can cause serious side effects, including:

- **fungal infection in your mouth or throat (thrush).** Rinse your mouth with water without swallowing after using BREO ELLIPTA to help reduce your chance of getting thrush.
- **pneumonia.** People with COPD have a higher chance of getting pneumonia. BREO ELLIPTA may increase the chance of getting pneumonia. Call your healthcare provider if you notice any of the following symptoms:
  - increase in mucus (sputum) production
  - change in mucus color
  - fever
  - chills
  - increased cough
  - increased breathing problems
- **weakened immune system and increased chance of getting infections (immunosuppression).**
- **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a condition where the adrenal glands do not make enough steroid hormones. This can happen when you stop taking oral corticosteroid medicines (such as prednisone) and start taking a medicine containing an ICS (such as BREO ELLIPTA). During this transition period, when your body is under stress from fever, trauma (such as a car accident), infection, surgery, or worse COPD or asthma symptoms, adrenal insufficiency can get worse and may cause death.

  Symptoms of adrenal insufficiency include:
  - feeling tired
  - lack of energy
  - weakness
  - nausea and vomiting
  - low blood pressure (hypotension)
- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop using BREO ELLIPTA and call your healthcare provider right away.
- **serious allergic reactions.** Call your healthcare provider or get emergency medical care if you get any of the following symptoms of a serious allergic reaction:
  - rash
  - hives
  - swelling of your face, mouth, and tongue
  - breathing problems
- **effects on heart.**
  - increased blood pressure
  - a fast or irregular heartbeat, awareness of heartbeat
  - chest pain
- **effects on nervous system.**
  - Tremor
  - Nervousness
- **bone thinning or weakness (osteoporosis).**
- **slowed growth in children.** A child's growth should be checked often.
- **eye problems** including glaucoma, increased pressure in your eye, cataracts, or other changes in vision. You should have regular eye exams while using BREO ELLIPTA.
- **changes in laboratory blood values**, including high levels of blood sugar (hyperglycemia) and low levels of potassium (hypokalemia).

Common side effects of BREO ELLIPTA include:

COPD:

- runny nose and sore throat
- upper respiratory tract infection
- headache
- bronchitis
- inflammation of the sinuses
- cough

- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
- back pain
- pneumonia
- mouth and throat pain
- joint pain
- increased blood pressure
- flu
- fever

Asthma:

- runny nose and sore throat
- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.
- headache
- flu
- respiratory tract infection
- bronchitis
- inflammation of the sinuses
- mouth and throat pain
- hoarseness and voice changes
- cough

These are not all the possible side effects of BREO ELLIPTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BREO ELLIPTA?

- Store BREO ELLIPTA at room temperature between 68°F and 77°F (20°C and 25°C). Keep in a dry place away from heat and sunlight.
- Store BREO ELLIPTA in the unopened tray and only open when ready for use.
- Safely throw away BREO ELLIPTA in the trash 6 weeks after you open the tray or when the counter reads “0”, whichever comes first. Write the date you open the tray on the label on the inhaler.

Keep BREO ELLIPTA and all medicines out of the reach of children.

General information about the safe and effective use of BREO ELLIPTA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use BREO ELLIPTA for a condition for which it was not prescribed. Do not give BREO ELLIPTA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about BREO ELLIPTA that is written for health professionals.

What are the ingredients in BREO ELLIPTA?

Active ingredients: fluticasone furoate, vilanterol trifenatate

Inactive ingredients: lactose monohydrate (contains milk proteins), magnesium stearate

For more information about BREO ELLIPTA, call 1-888-825-5249.

BREO ELLIPTA was developed in collaboration with Innoviva.

INNOVIVA

GlaxoSmithKline, Durham, NC 27701

BRE:xPIL

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: Month 20xx

INSTRUCTIONS FOR USE

BREO ELLIPTA (BRE-oh e-LIP-ta)

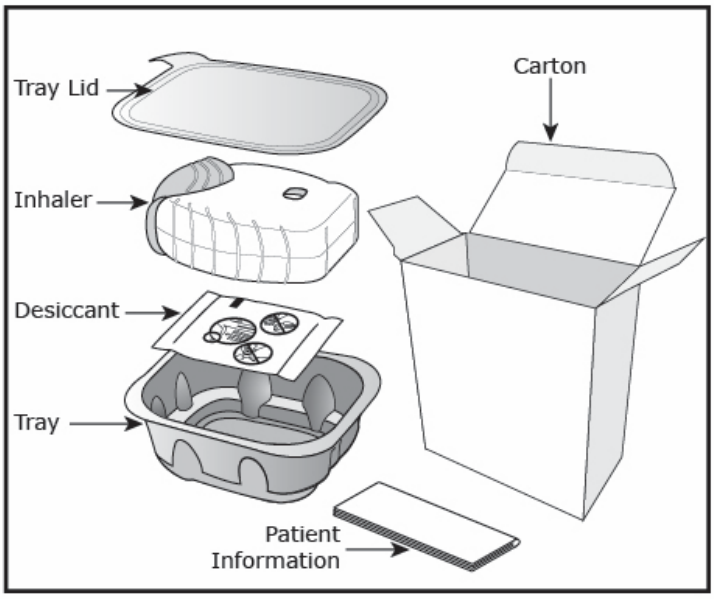
(fluticasone furoate and vilanterol inhalation powder)

for oral inhalation use

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 to be inhaled.**
- **It is not possible to accidentally take a double dose or an extra dose in 1 inhalation.**

Your BREO ELLIPTA inhaler



How to use your inhaler

- BREO ELLIPTA comes in a tray.
- Peel back the lid to open the tray. See **Figure A**.
- The tray contains a desiccant to reduce moisture. Do not eat or inhale. Throw it away in the household trash out of reach of children and pets. See **Figure B**.

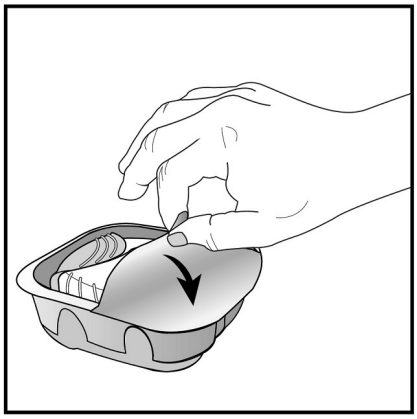


Figure A

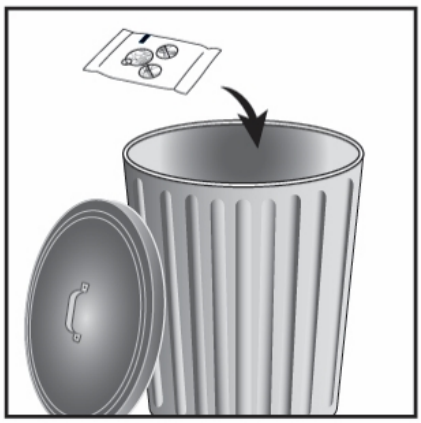


Figure B

Important Notes:

- Your inhaler contains 30 doses (14 doses if you have a sample or institutional pack).
- Each time you fully open the cover of the inhaler (you will hear a clicking sound), a dose is ready to be inhaled. This is shown by a decrease in the number on the counter.
- If you open and close the cover without inhaling the medicine, you will lose the dose. The lost dose will be held in the inhaler, but it will no longer be available to be inhaled. It is not possible to accidentally take a double dose or an extra dose in 1 inhalation.
- **Do not** open the cover of the inhaler until you are ready to use it. To avoid wasting doses after the inhaler is ready, **do not** close the cover until after you have inhaled the medicine.
- Write the “Tray opened” and “Discard” dates on the inhaler label. The “Discard” date is 6 weeks from the date you open the tray.

Check the counter. See Figure C.

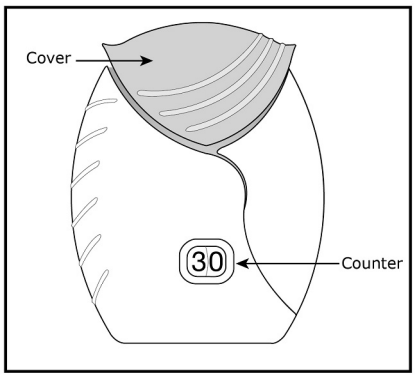


Figure C

- Before the inhaler is used for the first time, the counter should show the number 30 (14 if you have a sample or institutional pack). This is the number of doses in the inhaler.
- Each time you open the cover, you prepare 1 dose of medicine.
- The counter counts down by 1 each time you open the cover.

Prepare your dose:

Wait to open the cover until you are ready to take your dose.

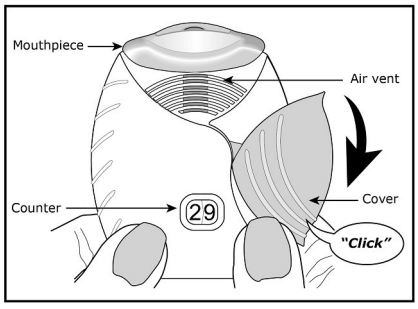


Figure D

Step 1. Open the cover of the inhaler. See Figure D.

- Slide the cover down to expose the mouthpiece. You should hear a “click.” The counter will count down by 1 number. You do not need to shake this kind of inhaler. **Your inhaler is now ready to use.**
- If the counter does not count down as you hear the click, the inhaler will not deliver the medicine. Call your healthcare provider or pharmacist if this happens.

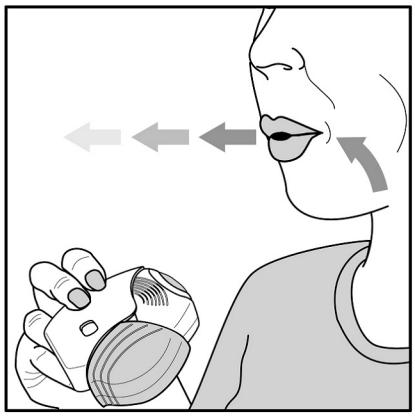


Figure E

Step 2. Breathe out. See Figure E.

- While holding the inhaler away from your mouth, breathe out (exhale) fully. Do not breathe out into the mouthpiece.

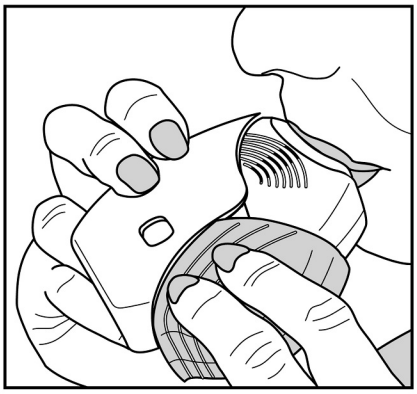


Figure F

Step 3. Inhale your medicine. See Figure F.

- Put the mouthpiece between your lips, and close your lips firmly around it. Your lips should fit over the curved shape of the mouthpiece.
- Take one long, steady, deep breath in through your mouth. **Do not** breathe in through your nose.

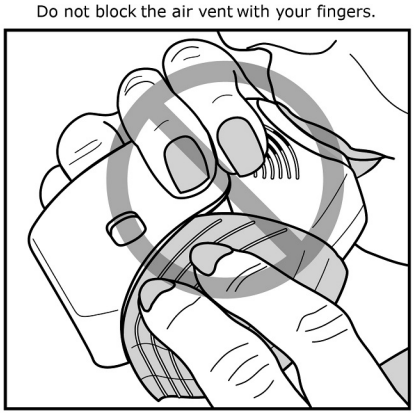


Figure G

- Do not block the air vent with your fingers. **See Figure G.**

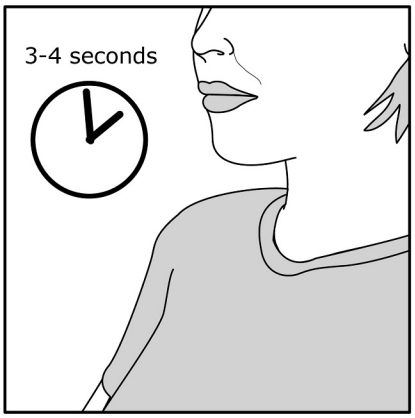


Figure H

- **Remove the inhaler from your mouth and hold your breath for about 3 to 4 seconds** (or as long as comfortable for you). **See Figure H.**

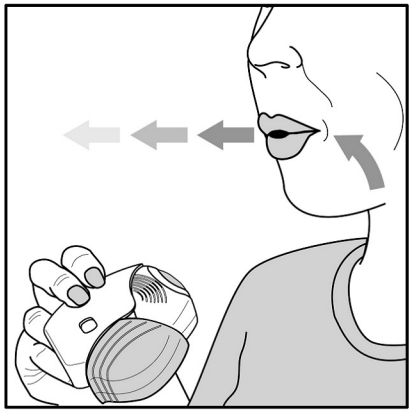


Figure I

Step 4. Breathe out slowly and gently. See Figure I.

- You may not taste or feel the medicine, even when you are using the inhaler correctly.
- **Do not** take another dose from the inhaler even if you do not feel or taste the medicine.

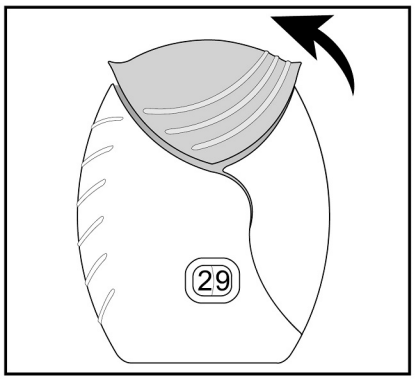


Figure J

Step 5. Close the inhaler. See Figure J.

- You can clean the mouthpiece if needed, using a dry tissue, before you close the cover. Routine cleaning is not required.
- Slide the cover up and over the mouthpiece as far as it will go.

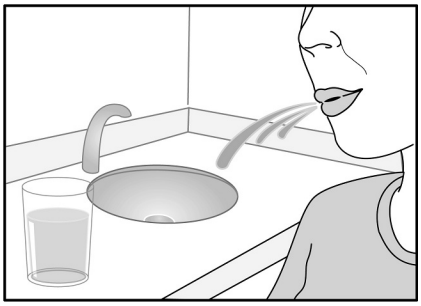


Figure K

Step 6. Rinse your mouth. See Figure K.

- Rinse your mouth with water after you have used the inhaler and spit the water out. **Do not** swallow the water.

Important Note: When should you get a refill?

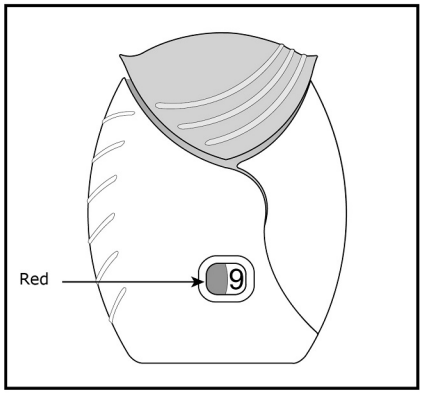


Figure L

- **When you have fewer than 10 doses remaining** in your inhaler, the left half of the counter shows red as a reminder to get a refill. **See Figure L.**
- After you have inhaled the last dose, the counter will show "0" and will be empty.
- Throw the empty inhaler away in your household trash out of reach of children and pets.

For more information about BREO ELLIPTA or how to use your inhaler, call 1-888-825-5249.
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