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 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation
BREO ELLIPTA 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), for oral inhalation
Initial U.S. Approval: 2013

WARNING: ASTHMA-RELATED DEATH
See full prescribing information for complete boxed warning.

- **Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths. This finding with salmeterol is considered a class effect of all LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. (5.1)**
- **When treating patients with asthma, only prescribe BREO ELLIPTA for patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO ELLIPTA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose ICS. (1.2, 5.1)**

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

- Long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1.1)
- Once-daily treatment of asthma in patients aged 18 years and older. (1.2)

Important limitation: Not indicated for relief of acute bronchospasm. (1.1, 1.2, 5.2)

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

- For oral inhalation only. (2)
- Maintenance treatment of COPD: 1 inhalation of BREO ELLIPTA 100/25 once daily. (2.1)
- Asthma: 1 inhalation of BREO ELLIPTA 100/25 or BREO ELLIPTA 200/25 once daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS----------
Inhalation Powder. Inhaler containing 2 foil blister strips of powder formulation for oral inhalation. One strip contains fluticasone furoate 100 or 200 mcg per blister and the other contains vilanterol 25 mcg per blister. (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 increase the risk of asthma-related death and asthma-related hospitalizations. Prescribe only for recommended patient populations. (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 an additional medicine 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. Taper 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)
- Close monitoring for glaucoma and cataracts is warranted. (5.14)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Be alert to hypokalemia and hyperglycemia. (5.16)

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

- COPD: Most common adverse reactions (incidence greater than or equal to 3%) are nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis. (6.1)
- Asthma: Most common adverse reactions (incidence greater than or equal to 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 vascular 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 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 Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of LABA. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids (ICS) or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Therefore, when treating patients with asthma, physicians should only prescribe BREO ELLIPTA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO ELLIPTA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids *[see Warnings and Precautions (5.1)]*.

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1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Chronic Obstructive Pulmonary Disease

BREO® ELLIPTA® 100/25 is a combination inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA) indicated for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. BREO ELLIPTA 100/25 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. BREO ELLIPTA 100/25 once daily is the only strength indicated for the treatment of COPD.

Important Limitation of Use

BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm

1.2 Treatment of Asthma

BREO ELLIPTA is a combination ICS/LABA indicated for the once-daily treatment of asthma in patients aged 18 years and older.

LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients *[see Warnings and Precautions (5.1), Adverse Reactions (6.2), Use in Specific Populations (8.4)]*. Therefore, when treating patients with asthma, physicians should only prescribe BREO ELLIPTA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO ELLIPTA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Important Limitation of Use

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

2 DOSAGE AND ADMINISTRATION

BREO ELLIPTA should be administered once daily every day by the orally inhaled route only.

BREO ELLIPTA should be taken at the same time every day. Do not use BREO ELLIPTA more than 1 time every 24 hours.

After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

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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. Patients using BREO ELLIPTA should not use additional LABA for any reason. *[See Warnings and Precautions (5.3, 5.5, 5.8, 5.12).]*

2.1 Chronic Obstructive Pulmonary Disease

BREO ELLIPTA 100/25 should be administered as 1 inhalation once daily. The maximum recommended dosage is 1 inhalation of BREO ELLIPTA 100/25 once daily, the only strength indicated for the treatment of COPD.

If shortness of breath occurs in the period between doses, an inhaled, short-acting beta$_2$-agonist (rescue medicine, e.g., albuterol) should be taken for immediate relief.

2.2 Asthma

If asthma symptoms arise in the period between doses, an inhaled, short-acting beta$_2$-agonist (rescue medicine, e.g., albuterol) should be taken for immediate relief.

The recommended starting dosage is BREO ELLIPTA 100/25 or BREO ELLIPTA 200/25 administered as 1 inhalation once daily. The maximum recommended dosage is 1 inhalation of BREO ELLIPTA 200/25 once daily.

The starting dosage is based on patients' asthma severity. For patients previously treated with low- to mid-dose corticosteroid–containing treatment, BREO ELLIPTA 100/25 should be considered. For patients previously treated with mid- to high-dose corticosteroid-containing treatment, BREO ELLIPTA 200/25 should be considered.

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, increasing the dose to BREO ELLIPTA 200/25 may provide additional improvement in asthma control.

If a previously effective dosage regimen of BREO ELLIPTA fails to provide adequate improvement in asthma control, the therapeutic regimen should be reevaluated and additional therapeutic options (e.g., replacing the current strength of BREO ELLIPTA with a higher strength, adding additional inhaled corticosteroid, initiating oral corticosteroids) should be considered.

3 DOSAGE FORMS AND STRENGTHS

Inhalation powder: Disposable light grey and pale blue plastic inhaler containing 2 foil blister strips of powder intended for oral inhalation only. One strip contains fluticasone furoate (100 or 200 mcg per blister), and the other strip contains vilanterol (25 mcg per blister).

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4 CONTRAINDICATIONS

The use of 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 Asthma-Related Death

LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe BREO ELLIPTA for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue BREO ELLIPTA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

A 28-week, placebo-controlled, US trial that compared the safety of another LABA (salmeterol) with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs. 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The increased risk of asthma-related death is considered a class effect of LABA, including vilanterol, one of the active ingredients in BREO ELLIPTA. No trial adequate to determine whether the rate of asthma-related death is increased in subjects treated with BREO ELLIPTA has been conducted.

Data are not available to determine whether the rate of death in patients with COPD is increased by LABA.

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 subjects

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with acutely deteriorating COPD or asthma. The initiation of BREO ELLIPTA in this setting is not appropriate.

COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If BREO ELLIPTA 100/25 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 a reevaluation of the patient and the COPD treatment regimen should be undertaken at once. For COPD, increasing the daily dose of BREO ELLIPTA 100/25 is not appropriate in this situation.

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 possible need for replacing the current strength of BREO ELLIPTA with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. 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 Excessive Use of BREO ELLIPTA and Use with Other Long-acting Beta$_2$-agonists

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

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with *Candida albicans* has occurred in subjects treated with BREO ELLIPTA. 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, but at times therapy with BREO ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

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5.5 Pneumonia

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

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

5.6 Immunosuppression

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

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

5.7 Transferring Patients from Systemic Corticosteroid Therapy

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. 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

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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 physicians 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.

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).

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 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 inhaled corticosteroids 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.

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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, BREO ELLIPTA should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids, and other treatments for management of COPD or asthma symptoms should be considered.

5.9 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the coadministration of BREO ELLIPTA with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., 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

As with other inhaled medicines, 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.

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)]*.

5.12 Cardiovascular Effects

Vilanterol, like other 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. 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. 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 subjects 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

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with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.13 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. 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 medicine to treat or prevent osteoporosis should be strongly considered.

5.14 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with COPD or asthma following the long-term administration of inhaled corticosteroids. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.15 Coexisting Conditions

BREO ELLIPTA, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis 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.

5.16 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medicines 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. Beta-agonist medications may produce transient hyperglycemia in some patients. In clinical trials evaluating BREO ELLIPTA in subjects with COPD or asthma, there was no evidence of a treatment effect on serum glucose or potassium.

5.17 Effect on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. *[See Use in Specific Populations (8.4).]*

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6 ADVERSE REACTIONS

LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Data from a large placebo-controlled US trial that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. *[See Warnings and Precautions (5.1).]*

Systemic and local corticosteroid use may result in the following:

- *Candida albicans* infection *[see Warnings and Precautions (5.4)]*
- Increased risk of pneumonia in COPD *[see Warnings and Precautions (5.5)]*
- Immunosuppression *[see Warnings and Precautions (5.6)]*
- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.8)]*
- Reduction in bone mineral density *[see Warnings and Precautions (5.13)]*

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 clinical program for BREO ELLIPTA included 7,700 subjects with COPD in two 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter duration. A total of 2,034 subjects with COPD received at least 1 dose of BREO ELLIPTA 100/25, and 1,087 subjects received a higher strength of fluticasone furoate/vilanterol. The safety data described below are based on the confirmatory 6- and 12-month trials. Adverse reactions observed in the other trials were similar to those observed in the confirmatory trials.

<u>6-Month Trials</u>

The incidence of adverse reactions associated with BREO ELLIPTA 100/25 in Table 1 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 subjects, 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%).

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

Table 1. Adverse Reactions with BREO ELLIPTA 100/25 with ≥3% Incidence and More Common than Placebo in Subjects with Chronic Obstructive Pulmonary Disease

Adverse Reaction	BREO ELLIPTA 100/25 (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 is 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 subjects, 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 subject population had moderate to very severely impaired airflow obstruction. Subjects received 1 inhalation once daily of the following: BREO ELLIPTA 100/25, BREO ELLIPTA 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg. In addition to the reactions shown in Table 1, adverse reactions occurring in greater than or equal to 3% of the subjects treated with BREO ELLIPTA 100/25 (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.

6.2 Clinical Trials Experience in Asthma

BREO ELLIPTA for the treatment of asthma was studied in 18 double-blind, parallel-group, controlled trials (11 with placebo) of 4 to 76 weeks' duration, which enrolled 9,969 subjects with asthma. BREO ELLIPTA 100/25 was studied in 2,369 subjects and BREO ELLIPTA 200/25 was studied in 956 subjects. While subjects aged 12 to 17 years were included in these trials, BREO ELLIPTA is not approved for use in this age group *[see Use in Specific Populations*

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(8.4)]. The safety data described below are based on two 12-week efficacy trials, one 24-week efficacy trial, and two long-term trials.

12-Week Trials

Trial 1 was a 12-week trial that evaluated the efficacy of BREO ELLIPTA 100/25 in adolescent and adult subjects with asthma compared with fluticasone furoate 100 mcg and placebo. Of the 609 subjects, 58% were female and 84% were white; the mean age was 40 years. The incidence of adverse reactions associated with BREO ELLIPTA 100/25 is shown in Table 2.

Table 2. Adverse Reactions with BREO ELLIPTA 100/25 with ≥2% Incidence and More Common than Placebo in Subjects with Asthma (Trial 1)

Adverse Reaction	BREO ELLIPTA 100/25 (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 2 was a 12-week trial that evaluated the efficacy of BREO ELLIPTA 100/25, BREO ELLIPTA 200/25, and fluticasone furoate 100 mcg in adolescent and adult subjects with asthma. This trial did not have a placebo arm. Of the 1,039 subjects, 60% were female and 88% were white; the mean age was 46 years. The incidence of adverse reactions associated with BREO ELLIPTA 100/25 and BREO ELLIPTA 200/25 is shown in Table 3.

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Table 3. Adverse Reactions with BREO ELLIPTA 100/25 and BREO ELLIPTA 200/25 with ≥2% Incidence in Subjects with Asthma (Trial 2)

Adverse Reaction	BREO ELLIPTA 200/25 (n = 346) %	BREO ELLIPTA 100/25 (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 3 was a 24-week trial that evaluated the efficacy of BREO ELLIPTA 200/25 once daily, fluticasone furoate 200 mcg once daily, and fluticasone propionate 500 mcg twice daily in adolescent and adult subjects with asthma. Of the 586 subjects, 59% were female and 84% were white; the mean age was 46 years. This trial did not have a placebo arm. In addition to the reactions shown in Tables 2 and 3, adverse reactions occurring in greater than or equal to 2% of subjects treated with BREO ELLIPTA 200/25 included viral respiratory tract infection, pharyngitis, pyrexia, and arthralgia.

12-Month Trial

Long-term safety data is based on a 12-month trial that evaluated the safety of BREO ELLIPTA 100/25 once daily (n = 201), BREO ELLIPTA 200/25 once daily (n = 202), and fluticasone propionate 500 mcg twice daily (n = 100) in adolescent and adult subjects with asthma (Trial 4). Overall, 63% were female and 67% were white. The mean age was 39 years; adolescents (aged 12 to 17 years) made up 16% of the population. In addition to the reactions shown in Tables 2 and 3, adverse reactions occurring in greater than or equal to 2% of the subjects treated with BREO ELLIPTA 100/25 or BREO ELLIPTA 200/25 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.

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Exacerbation Trial

In a 24- to 76-week trial, subjects received BREO ELLIPTA 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010) (Trial 5). Subjects participating in this trial had a history of one 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. Overall, 67% were female and 73% were white; the mean age was 42 years (adolescents aged 12 to 17 years made up 14% of the population). While subjects aged 12 to 17 years were included in this trial, BREO ELLIPTA is not approved for use in this age group *[see Use in Specific Populations (8.4)]*. Asthma-related hospitalizations occurred in 10 subjects (1%) treated with BREO ELLIPTA 100/25 compared with 7 subjects (0.7%) treated with fluticasone furoate 100 mcg. Among subjects aged 12 to 17 years, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO ELLIPTA 100/25 (n = 151) compared with 0 subjects treated with fluticasone furoate 100 mcg (n = 130). There were no asthma-related deaths or asthma-related intubations observed in this trial.

6.3 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postapproval 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.

Musculoskeletal and Connective Tissue Disorders

Muscle spasms.

Nervous System Disorders

Tremor.

Psychiatric Disorders

Nervousness.

Respiratory, Thoracic, and Mediastinal Disorders

Paradoxical bronchospasm.

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7 DRUG INTERACTIONS

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone furoate and vilanterol, the individual components of BREO ELLIPTA, 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 long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) *[see Warnings and Precautions (5.9), Clinical Pharmacology (12.3)]*.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

Vilanterol, like other beta$_2$-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval 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, a component of BREO ELLIPTA, 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

<u>Teratogenic Effects</u>

Pregnancy Category C. There are no adequate and well-controlled trials with BREO ELLIPTA in pregnant women. Corticosteroids and beta$_2$-agonists have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Because

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animal reproduction studies are not always predictive of human response, BREO ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women should be advised to contact their physicians if they become pregnant while taking BREO ELLIPTA.

Fluticasone Furoate and Vilanterol: There was no evidence of teratogenic interactions between fluticasone furoate and vilanterol in rats at approximately 5 and 40 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mcg/m^2 basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in combination, up to approximately 95 mcg/kg/day).

Fluticasone Furoate: There were no teratogenic effects in rats and rabbits at approximately 4 and 1 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were no effects on perinatal and postnatal development in rats at approximately 1 time the MRHDID in adults (on a mcg/m^2 basis at maternal doses up to 27 mcg/kg/day).

Vilanterol: There were no teratogenic effects in rats and rabbits at approximately 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m^2 basis at maternal inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at approximately 1,000 times the MRHDID in adults (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. There were no effects on perinatal and postnatal development in rats at approximately 3,900 times the MRHDID in adults (on a mcg/m^2 basis at maternal oral doses up to 10,000 mcg/kg/day).

Nonteratogenic Effects

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

8.2 Labor and Delivery

There are no adequate and well-controlled human trials that have investigated the effects of BREO ELLIPTA during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, BREO ELLIPTA should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

It is not known whether fluticasone furoate or vilanterol are excreted in human breast milk. However, other corticosteroids and $beta_2$-agonists have been detected in human milk. Since there are no data from controlled trials on the use of BREO ELLIPTA by nursing mothers, caution should be exercised when it is administered to a nursing woman.

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8.4 Pediatric Use

BREO ELLIPTA is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.

In a 24- to 76-week exacerbation trial, subjects received BREO ELLIPTA 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a mean age of 42 years and a history of one 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 study entry. *[See Clinical Studies (14.2).]* Adolescents aged 12 to 17 years made up 14% of the study population (n = 281), with a mean exposure of 352 days for subjects in this age group treated with BREO ELLIPTA 100/25 (n = 151) and 355 days for subjects in this age group treated with fluticasone furoate 100 mcg (n = 130). In this age group, 10% of subjects treated with BREO ELLIPTA 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO ELLIPTA 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age group.

<u>Effects on Growth</u>

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

Controlled clinical trials have shown that inhaled corticosteroids 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 children and adolescents 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.

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A randomized, double-blind, parallel-group, multicenter, 1-year, placebo-controlled trial evaluated the effect of once-daily treatment with 110 mcg of fluticasone furoate in the nasal spray formulation on growth velocity assessed by stadiometry. The subjects were 474 prepubescent children (girls aged 5 to 7.5 years and boys aged 5 to 8.5 years). Mean growth velocity over the 52-week treatment period was lower in the subjects receiving fluticasone furoate nasal spray (5.19 cm/year) compared with placebo (5.46 cm/year). The mean reduction in growth velocity was 0.27 cm/year (95% CI: 0.06 to 0.48) *[see Warnings and Precautions (5.17)]*.

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 2,508 subjects aged 65 and older and 564 subjects aged 75 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 subjects.

8.6 Hepatic Impairment

Fluticasone furoate systemic exposure increased by up to 3-fold in subjects 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 *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

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

10 OVERDOSAGE

No human overdosage data has been reported for BREO ELLIPTA.

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.

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10.1 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)]*.

Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of 500 mcg or higher given once daily for 14 days.

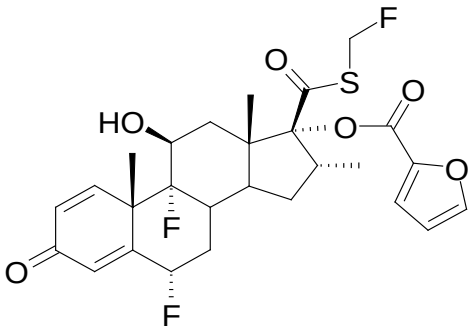
10.2 Vilanterol

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 100/25 and BREO ELLIPTA 200/25 are inhalation powders for oral inhalation that contain a combination of fluticasone furoate (an ICS) and vilanterol (a LABA).

One active component of BREO ELLIPTA is fluticasone furoate, a synthetic trifluorinated corticosteroid having 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.

The other active component of BREO ELLIPTA is vilanterol trifenatate, a LABA with the chemical name triphenylacetic acid-4-{(1*R*)-2-[(6-{2-[2,6-dicholorobenzyl)oxy]ethoxy}

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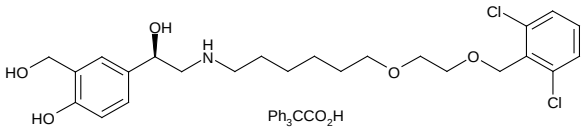
hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1) and the following chemical structure:



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 mix of micronized fluticasone furoate (100 or 200 mcg) and lactose monohydrate (12.4 mg), and each blister on the other strip contains a white powder mix 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 92 and 184 mcg of fluticasone furoate and 22 mcg of vilanterol per blister when tested at a flow rate of 60 L/min for 4 seconds.

In adult subjects with obstructive lung disease and severely compromised lung function (COPD with FEV_1/FVC less than 70% and FEV_1 less than 30% predicted or FEV_1 less than 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 subjects with severe asthma, mean peak inspiratory flow through the ELLIPTA inhaler was 96.6 L/min (range: 72.4 to 124.6 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

<u>BREO ELLIPTA</u>

Since 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 (a synthetic corticosteroid and a LABA) that have different effects on clinical and physiological indices.

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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 $beta_2$-adrenoceptor 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

Cardiovascular Effects

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 mcg/25 mcg and fluticasone furoate/vilanterol 800 mcg/100 mcg, respectively.

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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 mcg/25 mcg and fluticasone furoate/vilanterol 800 mcg/100 mcg, respectively.

HPA 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.

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

Subjects with Asthma: A randomized, double-blind, parallel-group trial in 185 subjects with asthma showed no difference between once-daily treatment with fluticasone furoate/vilanterol 100 mcg/25 mcg or fluticasone furoate/vilanterol 200 mcg/25 mcg compared with placebo on serum cortisol weighted mean (0 to 24 hours), serum cortisol $AUC_{(0-24)}$, 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 administrated 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 subjects 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

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vilanterol when administrated 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 (less than 2%) due to extensive first-pass metabolism. Systemic exposure (AUC) in subjects with COPD was 24% higher than observed in healthy subjects. Systemic exposure (AUC) in subjects 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 (99.6%).

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 93.9%.

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.

Elimination

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% of the recovered radioactive dose, respectively). The plasma elimination half-life of vilanterol, as determined from inhalation administration of multiple doses of vilanterol 25 mcg, is 21.3 hours in subjects with COPD and 16.0 hours in subjects with asthma.

Special Populations

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

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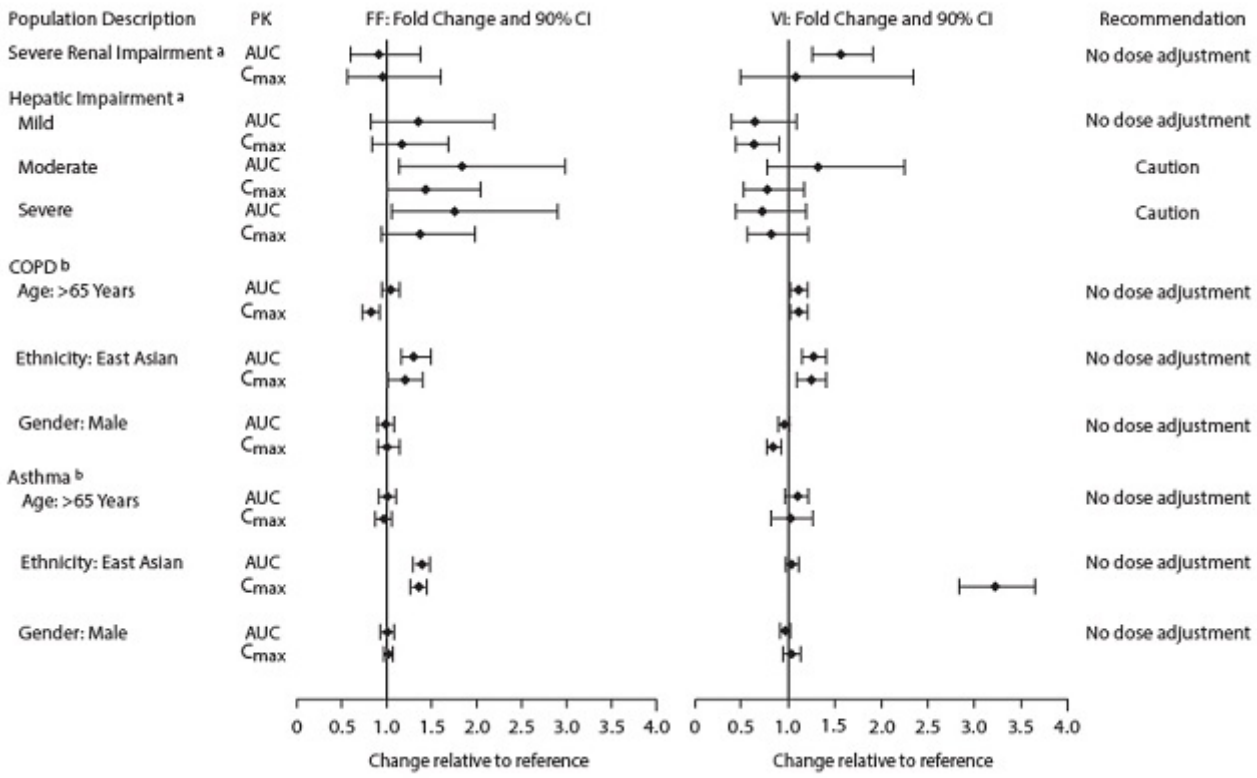
Figure 1. Impact of Intrinsic Factors on the Pharmacokinetics (PK) of Fluticasone Furoate (FF) and Vilanterol (VI) Following Administration as Fluticasone Furoate/Vilanterol Combination



[a] Severe renal impairment (CrCl less than 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 less than or equal to 65 years, gender compared with female, and ethnicity compared with white.

Race: 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 subjects 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.

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

Hepatic Impairment: Fluticasone Furoate: Following repeat dosing of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for

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7 days, there was an increase of 34%, 83%, and 75% in fluticasone furoate systemic exposure (AUC) in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with healthy subjects (Figure 1).

In subjects with moderate hepatic impairment receiving fluticasone furoate/vilanterol 200 mcg/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% (90% CI: 11%, 51%) compared with healthy subjects. In subjects with severe hepatic impairment receiving fluticasone furoate/vilanterol 100 mcg/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 mcg/25 mcg (100 mcg/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 subjects with mild or moderate hepatic impairment (vilanterol 25 mcg combination) or with severe hepatic impairment (vilanterol 12.5 mcg combination) compared with healthy subjects.

Renal Impairment: Fluticasone furoate systemic exposure was not increased and vilanterol systemic exposure [$AUC_{(0-24)}$] was 56% higher in subjects 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 subjects with severe renal impairment compared with healthy subjects.

Drug Interactions

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.

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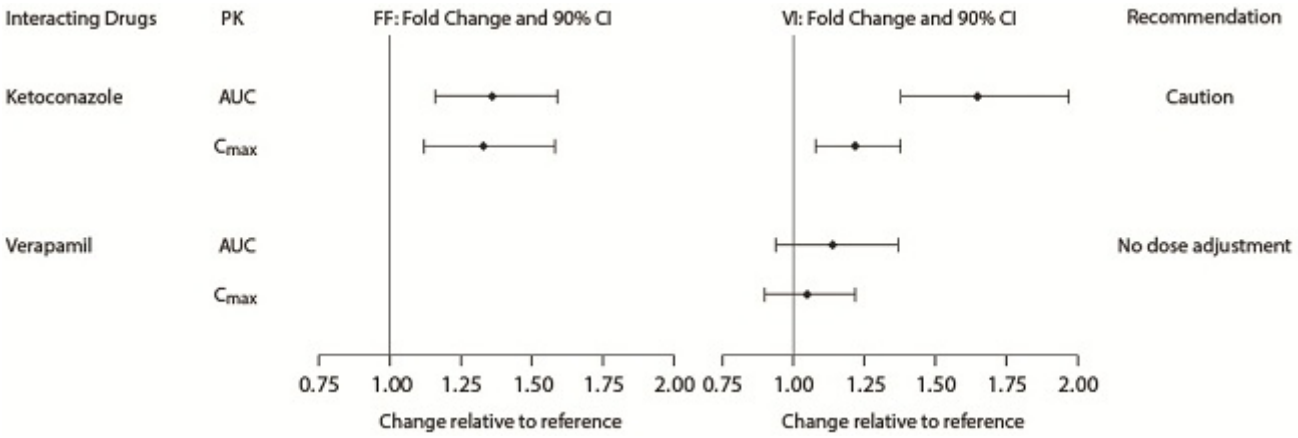
Figure 2. Impact of Coadministered Drugs[a] on the Pharmacokinetics (PK) of Fluticasone Furoate (FF) and Vilanterol (VI) Following Administration as Fluticasone Furoate/Vilanterol Combination or Vilanterol Coadministered with a Long-acting Muscarinic Antagonist



[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 potent P-gp inhibitor and moderate CYP3A4 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 (approximately 0.5 times the MRHDID in adults 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.

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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 1 and 4 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

Vilanterol

In a 2-year carcinogenicity study in mice, vilanterol caused a statistically significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of 29,500 mcg/kg/day (approximately 8,750 times the MRHDID in adults on an AUC basis). No increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 530 times the MRHDID in adults 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 inhalation doses greater than or equal to 84.4 mcg/kg/day (greater than or equal to approximately 45 times the MRHDID in adults on an AUC basis). No tumors were seen at an inhalation dose of 10.5 mcg/kg/day (approximately 2 times the MRHDID in adults 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 reproductive studies conducted in male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day, respectively (approximately 12,000 and 14,000 times, respectively, the MRHDID in adults on a mcg/m^2 basis).

14 CLINICAL STUDIES

14.1 Chronic Obstructive Pulmonary Disease

The safety and efficacy of BREO ELLIPTA were evaluated in 7,700 subjects with COPD. The development program included 4 confirmatory trials of 6 and 12 months' duration, three 12-week active comparator trials with fluticasone propionate/salmeterol 250 mcg/50 mcg, and dose-ranging trials of shorter duration. The efficacy of BREO ELLIPTA is based primarily on the dose-ranging trials and the 4 confirmatory trials described below.

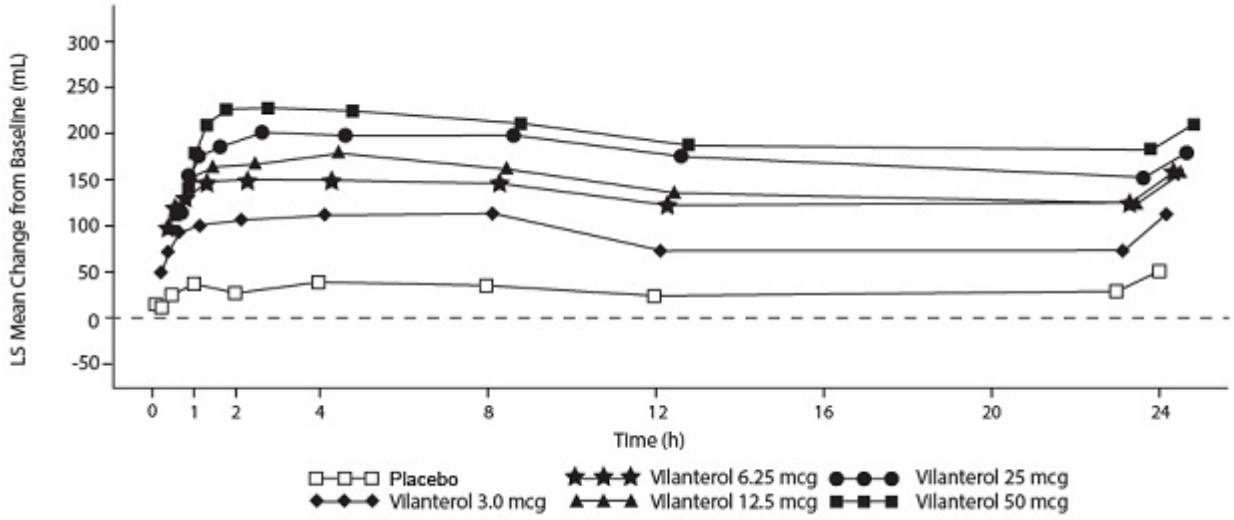
Dose Selection for Vilanterol

Dose selection for vilanterol in COPD was supported by a 28-day, randomized, double-blind, placebo-controlled, parallel-group trial evaluating 5 doses of vilanterol (3 to 50 mcg) or placebo dosed in the morning in 602 subjects with COPD. Results demonstrated dose-related increases from baseline in FEV_1 at Day 1 and Day 28 (Figure 3).

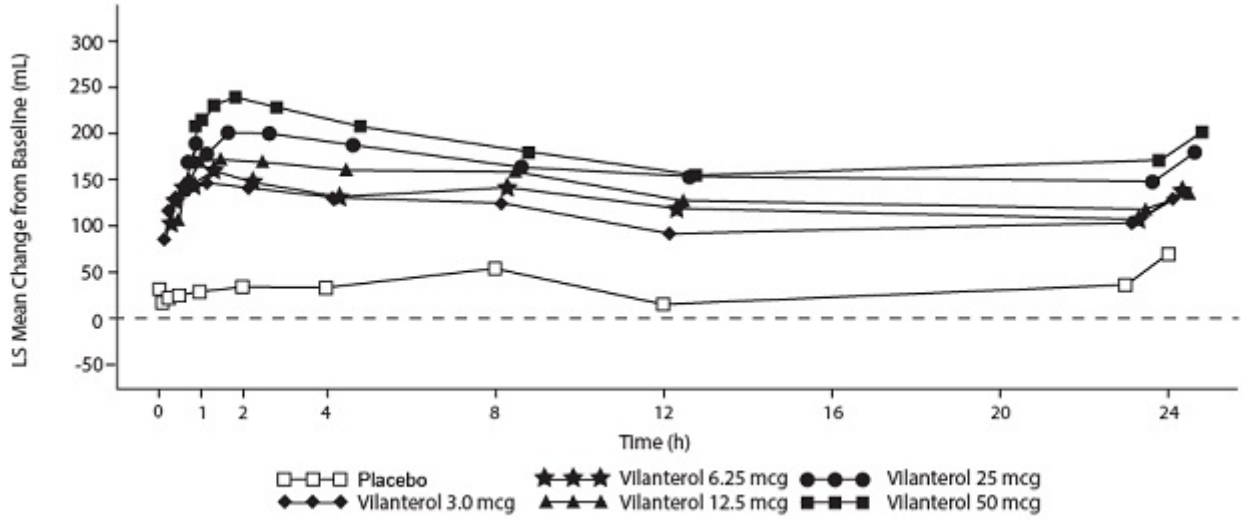
Reference ID: 4006672

Figure 3. Least Squares (LS) Mean Change from Baseline in Postdose Serial FEV_1 (0-24 h) (mL) on Days 1 and 28

Day 1



Day 28



The differences in trough FEV_1 on Day 28 from placebo for the 3-, 6.25-, 12.5-, 25-, and 50-mcg doses were 92 mL (95% CI: 39, 144), 98 mL (95% CI: 46, 150), 110 mL (95% CI: 57, 162), 137 mL (95% CI: 85, 190), and 165 mL (95% CI: 112, 217), respectively. These results supported the evaluation of vilanterol 25 mcg once daily in the confirmatory trials for COPD.

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Dose Selection for Fluticasone Furoate

Dose selection of fluticasone furoate for Phase III trials in subjects with COPD was based on dose-ranging trials conducted in subjects with asthma; these trials are described in detail below *[see Clinical Studies (14.2)]*.

Confirmatory Trials

The 4 confirmatory trials evaluated the efficacy of BREO ELLIPTA on lung function (Trials 1 and 2) and exacerbations (Trials 3 and 4).

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 subjects with COPD. In Trial 1, subjects were randomized to BREO ELLIPTA 100/25, BREO ELLIPTA 200/25, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, and placebo. In Trial 2, subjects were randomized to BREO ELLIPTA 100/25, fluticasone furoate/vilanterol 50 mcg/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 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 4).

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

[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 4. Similar results were seen in Trial 2 (not shown).

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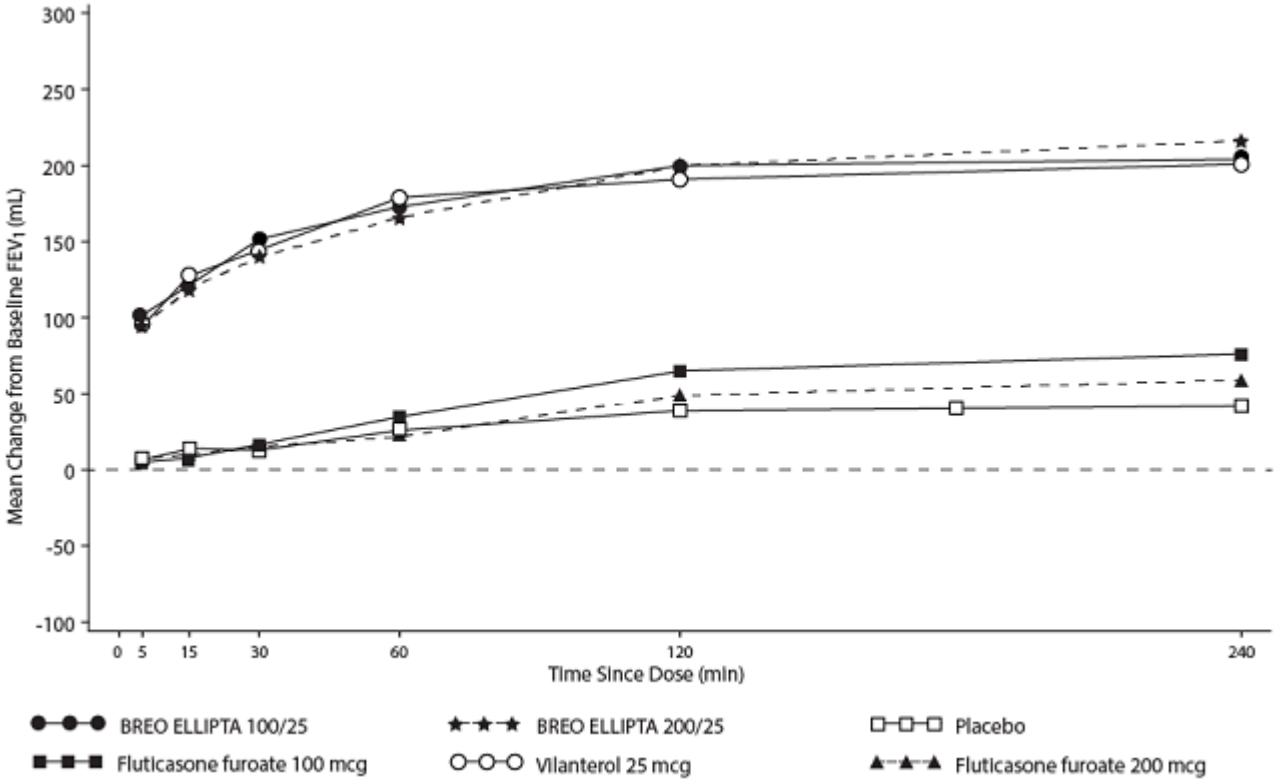
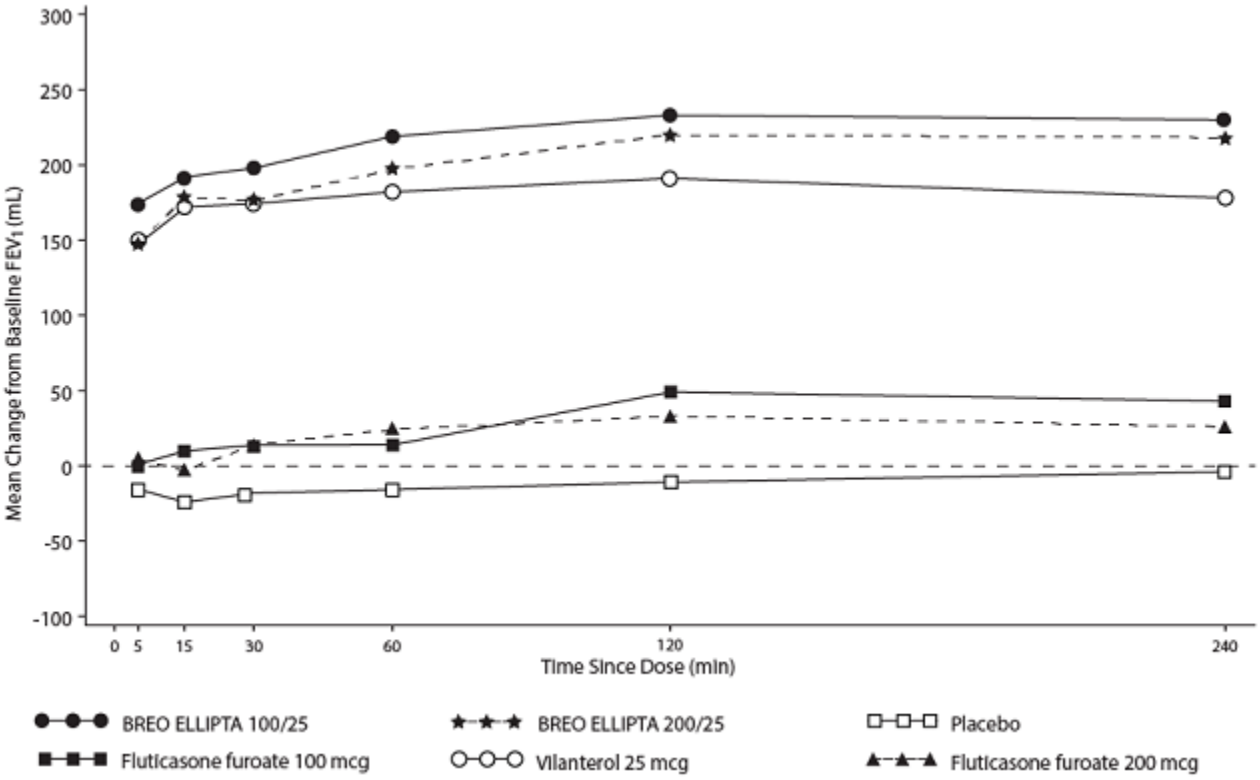
Figure 4. Raw Mean Change from Baseline in Postdose Serial FEV_1 (0-4 h) (mL) on Days 1 and 168

Day 1



Reference ID: 4006672

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 4). The comparison of BREO ELLIPTA 100/25 with vilanterol did not achieve statistical significance (Table 4).

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 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 subjects receiving BREO ELLIPTA 100/25.

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 subjects were treated with fluticasone propionate/salmeterol 250 mcg/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, BREO ELLIPTA 200/25, fluticasone furoate/vilanterol 50 mcg/25 mcg, or vilanterol 25 mcg.

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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 subjects, 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 subject population had moderate to very severely impaired airflow obstruction. The mean percent reversibility was 15% (range: -65% to 313%).

Subjects treated with BREO ELLIPTA 100/25 had a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol in both trials (Table 5).

Table 5. 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	403	0.90	0.79	0.64, 0.97
BREO ELLIPTA 200/25	409	0.79	0.69	0.56, 0.85
Fluticasone furoate/vilanterol 50 mcg/25 mcg	412	0.92	0.81	0.66, 0.99
Vilanterol 25 mcg	409	1.14	—	—
Trial 4				
BREO ELLIPTA 100/25	403	0.70	0.66	0.54, 0.81
BREO ELLIPTA 200/25	402	0.90	0.85	0.70, 1.04
Fluticasone furoate/vilanterol 50 mcg/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 once daily versus fluticasone propionate/salmeterol 250 mcg/50 mcg twice daily to evaluate the efficacy of serial lung function of BREO ELLIPTA in subjects with COPD.

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The primary endpoint of each study was change from baseline in weighted mean FEV_1 (0 to 24 hours) on Day 84. Of the 519 patients in Trial 5, 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, 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 mcg/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, 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, 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 mcg/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, 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, 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 mcg/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 was 174 (15) mL compared with 94 (16) mL with fluticasone propionate/salmeterol 250 mcg/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 was 142 (18) mL and 168 (12) mL, respectively, compared with 114 (18) mL and 142 (12) mL, respectively, for fluticasone propionate/salmeterol 250 mcg/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; $P = 0.137$).

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14.2 Asthma

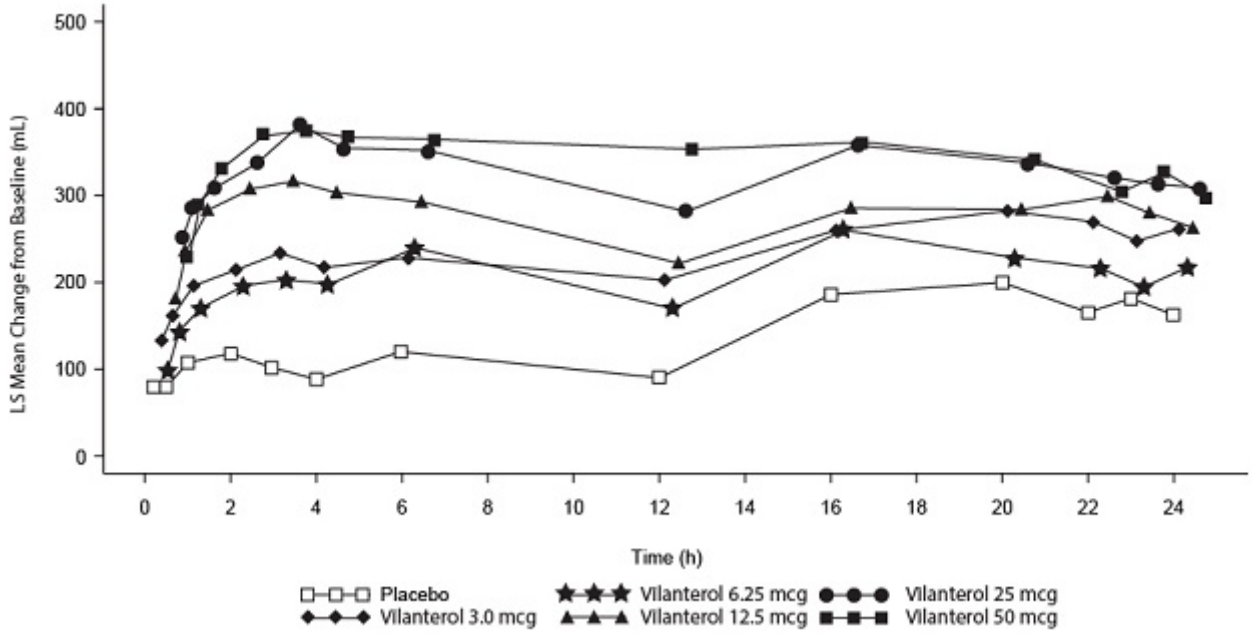
The safety and efficacy of BREO ELLIPTA were evaluated in 9,969 subjects with asthma. The development program included 4 confirmatory trials (2 of 12 weeks' duration, 1 of 24 weeks' duration, 1 exacerbation trial of 24 to 76 weeks' duration), one 24-week active comparator trial with fluticasone propionate/salmeterol 250 mcg/50 mcg, and dose-ranging trials of shorter duration. The efficacy of BREO ELLIPTA is based primarily on the dose-ranging trials and the 4 confirmatory trials described below.

Dose Selection for Vilanterol

Dose selection for vilanterol in asthma was supported by a 28-day, randomized, double-blind, placebo-controlled, parallel-group trial evaluating 5 doses of vilanterol (3 to 50 mcg) or placebo dosed in the evening in 607 subjects with asthma. Results demonstrated dose-related increases from baseline in FEV_1 at Day 1 and Day 28 (Figure 5).

Figure 5. Least Squares (LS) Mean Change from Baseline in Postdose Serial FEV_1 (0-24 h) (mL) on Days 1 and 28

Day 1



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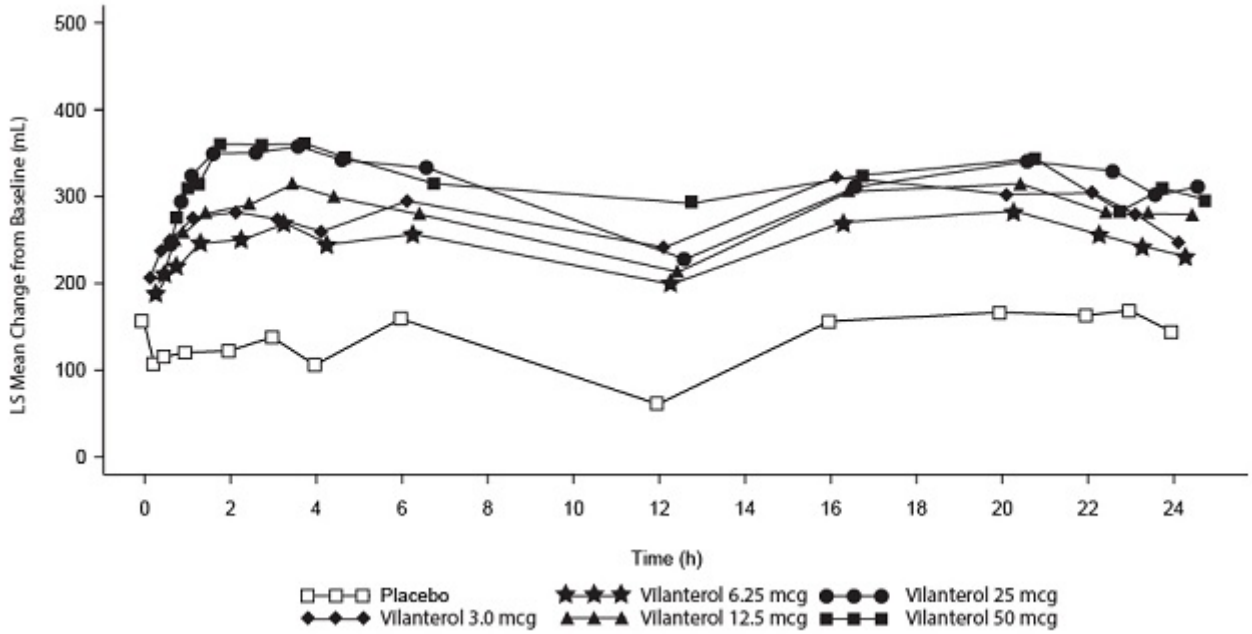
Day 28



The differences in trough FEV_1 on Day 28 from placebo for the 3-, 6.25-, 12.5-, 25-, and 50-mcg doses were 64 mL (95% CI: -36, 164), 69 mL (95% CI: -29, 168), 130 mL (95% CI: 30, 230), 121 mL (95% CI: 23, 220), and 162 mL (95% CI: 62, 261), respectively. These results and results of the secondary endpoints supported the evaluation of vilanterol 25 mcg once daily in the confirmatory trials for asthma.

Dose Selection for Fluticasone Furoate

Eight doses of fluticasone furoate ranging from 25 to 800 mcg once daily were evaluated in 3 randomized, double-blind, placebo-controlled, 8-week trials in subjects with asthma. A dose-related increase in trough FEV_1 at Week 8 was seen for doses from 25 to 200 mcg with no consistent additional benefit for doses above 200 mcg. To evaluate dosing frequency, a separate trial compared fluticasone furoate 200 mcg once daily and fluticasone furoate 100 mcg twice daily. The results supported the selection of the once-daily dosing frequency (Figure 6).

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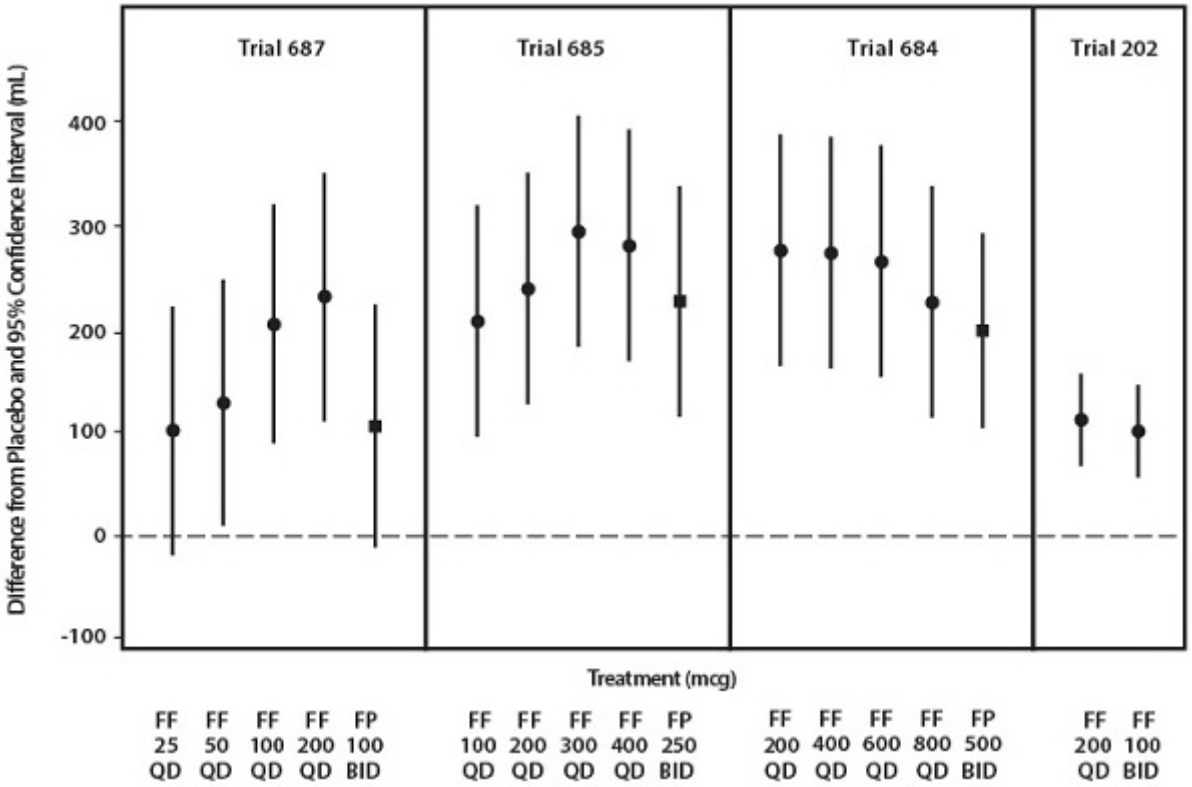
Figure 6. Fluticasone Furoate Dose-Ranging and Dose-Frequency Trials



FF = fluticasone furoate, FP = fluticasone propionate, QD = once daily, BID = twice daily.

Confirmatory Trials

The efficacy of BREO ELLIPTA was evaluated in 4 randomized, double-blind, parallel-group clinical trials in adolescent and adult subjects with asthma. Three trials were designed to evaluate the safety and efficacy of BREO ELLIPTA given once daily in subjects who were not controlled on their current treatments of inhaled corticosteroid or combination therapy consisting of an inhaled corticosteroid plus a LABA (Trials 1, 2, and 3). A 24- to 76-week exacerbation trial was designed to demonstrate that treatment with BREO ELLIPTA 100/25 significantly decreased the risk of asthma exacerbations as measured by time to first asthma exacerbation when compared with fluticasone furoate 100 mcg (Trial 5). This trial enrolled subjects who had one or more asthma exacerbations in the year prior to trial entry. The demographics of these 4 trials and the comparator trial (Trial 6) are provided in Table 6. While subjects aged 12 to 17 years were included in these trials, BREO ELLIPTA is not approved for use in this age group *[see Indications (1.2), Adverse Reactions (6.2), Use in Specific Populations (8.4)]*.

Reference ID: 4006672

Table 6. Demography of Asthma Trials 1, 2, 3, 5, and 6

Parameter	Trial 1 n = 609	Trial 2 n = 1,039	Trial 3 n = 586	Trial 5 n = 2,019	Trial 6 n = 806
Mean age (years) (range)	40 (12, 84)	46 (12, 82)	46 (12, 76)	42 (12, 82)	43 (12, 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 less than 10 packs per year history.

Trials 1, 2, and 3 were 12- or 24-week trials that evaluated the efficacy of BREO ELLIPTA on lung function in subjects with asthma. In Trial 1, subjects were randomized to BREO ELLIPTA 100/25, fluticasone furoate 100 mcg, or placebo. In Trial 2, subjects were randomized to BREO ELLIPTA 100/25, BREO ELLIPTA 200/25, or fluticasone furoate 100 mcg. In Trial 3, subjects were randomized to BREO ELLIPTA 200/25, 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. Subjects receiving an inhaled corticosteroid or an inhaled corticosteroid plus a LABA (doses of inhaled corticosteroid varied by trial and asthma severity) entered a 4-week run-in period during which LABA treatment was stopped. Subjects reporting symptoms and/or rescue $beta_2$-agonist medication use during the run-in period were continued in the trial.

In Trials 1 and 3, 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 2, 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. (See Table 7.) Weighted mean FEV_1 (0 to 24 hours) was derived from serial measurements taken within 30 minutes prior to dosing and postdose assessments at 5, 15, and

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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 7. Change from Baseline in Weighted Mean FEV_1 (0-24 h) (mL) and Trough FEV_1 (mL) at Study Endpoint (Trials 1, 2, and 3)

Study (Duration) Background Treatment		Weighted Mean FEV_1 (0-24 h) (mL)		
		Difference from		
Treatment	n	Placebo (95% CI)	Fluticasone Furoate 100 mcg (95% CI)	Fluticasone Furoate 200 mcg (95% CI)
Trial 1 (12 Weeks) Low- to mid-dose ICS or low-dose ICS + LABA				
BREO ELLIPTA 100/25	108	302 (178, 426)	116 (-5, 236)	—
Trial 2 (12 Weeks) Mid- to high-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 100/25	312	—	108 (45, 171)	—
Trial 3 (24 Weeks) High-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 200/25	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 1 (12 Weeks) Low- to mid-dose ICS or low-dose ICS + LABA				
BREO ELLIPTA 100/25	200	172 (87, 258)	36 (-48, 120)	—
Trial 2 (12 Weeks) Mid- to high-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 100/25	334	—	77 (16, 138)	—

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Trial 3 (24 Weeks) High-dose ICS or mid-dose ICS + LABA				
BREO ELLIPTA 200/25	187	—	—	193 (108, 277)

ICS = inhaled corticosteroid, LABA = long-acting beta$_2$-adrenergic agonist.

In Trial 1, weighted mean FEV_1 (0 to 24 hours) was assessed in a subset of subjects (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 compared with placebo (302 mL; 95% CI: 178, 426; $P<0.001$) (Table 7); change from baseline in weighted mean FEV_1 (0 to 24 hours) for BREO ELLIPTA 100/25 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 compared with placebo (172 mL; 95% CI: 87, 258; $P<0.001$) (Table 7); change from baseline in trough FEV_1 for BREO ELLIPTA 100/25 was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (36 mL; 95% CI: -48, 120).

In Trial 2, the change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for BREO ELLIPTA 100/25 compared with fluticasone furoate 100 mcg (108 mL; 95% CI: 45, 171; $P<0.001$) at Week 12 (Table 7). In a descriptive analysis, the change from baseline in weighted mean FEV_1 (0 to 24 hours) for BREO ELLIPTA 200/25 was numerically greater than BREO ELLIPTA 100/25 (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 compared with fluticasone furoate 100 mcg (77 mL, 95% CI: 16, 138; $P = 0.014$) at Week 12 (Table 7). In a descriptive analysis, the change from baseline in trough FEV_1 for BREO ELLIPTA 200/25 was numerically greater than BREO ELLIPTA 100/25 (16 mL; 95% CI: -46, 77) at Week 12.

In Trial 3, the change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for BREO ELLIPTA 200/25 compared with fluticasone furoate 200 mcg (136 mL; 95% CI: 1, 270; $P = 0.048$) at Week 24 (Table 7). The change from baseline in trough FEV_1 was significantly greater for BREO ELLIPTA 200/25 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 2 and 3. 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 2 in Figure 7.

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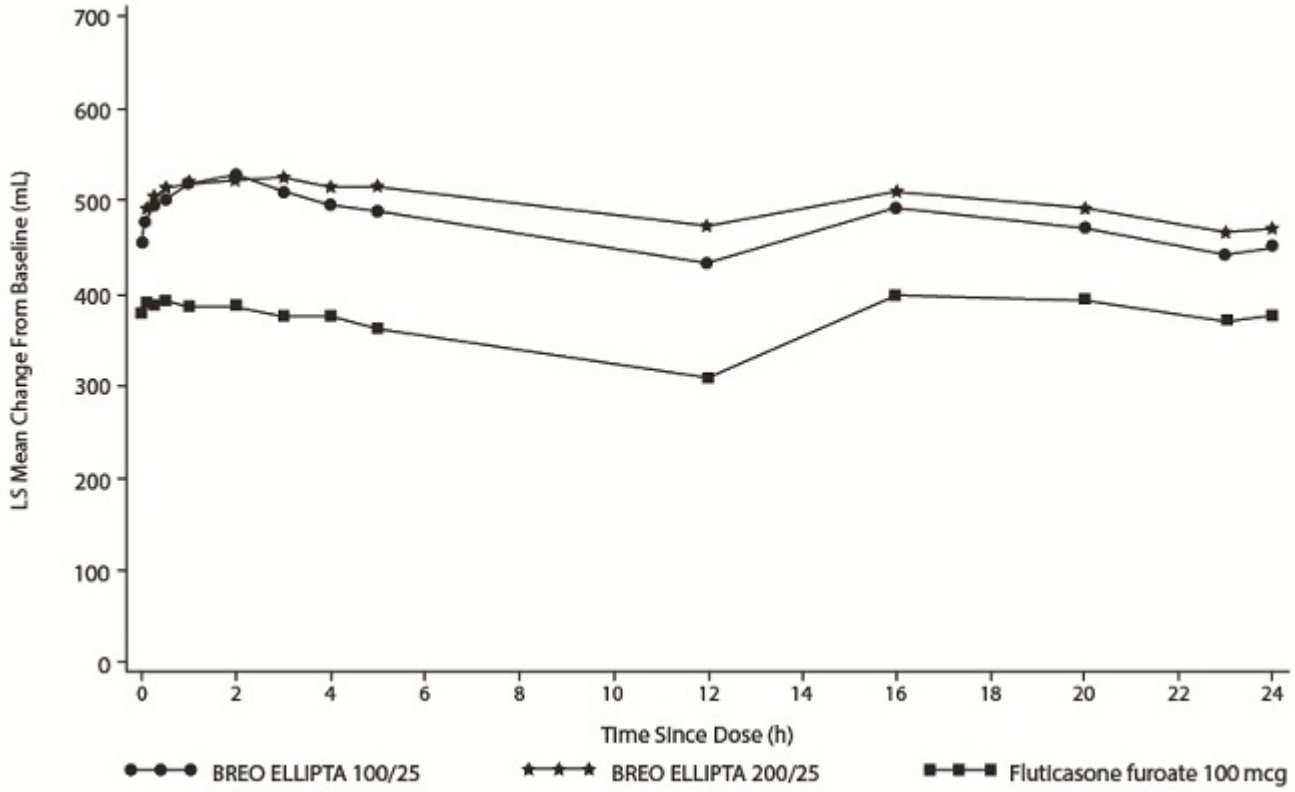
Figure 7. Least Squares (LS) Mean Change from Baseline in Individual Serial FEV_1 (mL) Assessments over 24 Hours after 12 Weeks of Treatment (Trial 2)



Subjects receiving BREO ELLIPTA 100/25 (Trial 2) or BREO ELLIPTA 200/25 (Trial 3) 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 subjects receiving fluticasone furoate 100 mcg or fluticasone furoate 200 mcg, respectively. In a descriptive analysis (Trial 2), subjects receiving BREO ELLIPTA 200/25 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 subjects receiving BREO ELLIPTA 100/25.

Trial 5 was a 24- to 76-week event-driven exacerbation trial that evaluated whether BREO ELLIPTA 100/25 significantly decreased the risk of asthma exacerbations as measured by time to first asthma exacerbation when compared with fluticasone furoate 100 mcg in subjects with asthma. Subjects receiving low- to high-dose inhaled corticosteroid (fluticasone propionate 100 mcg to 500 mcg twice daily or equivalent) or low- to mid-dose inhaled corticosteroid plus a LABA (fluticasone propionate/salmeterol 100 mcg/50 mcg to 250 mcg/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

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LABA treatment was stopped. Subjects 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 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 subjects treated with BREO ELLIPTA 100/25 compared with fluticasone furoate 100 mcg (P = 0.036). Mean yearly rates of asthma exacerbations of 0.14 and 0.19 in subjects treated with BREO ELLIPTA 100/25 compared with fluticasone furoate 100 mcg, respectively, were observed (25% reduction in rate; 95% CI: 5%, 40%).

Comparator Trial

Trial 6 was a 24-week trial that compared the efficacy of BREO ELLIPTA 100/25 once daily with fluticasone propionate/salmeterol 250 mcg/50 mcg twice daily (N = 806). Subjects receiving mid-dose inhaled corticosteroid (fluticasone propionate 250 mcg twice daily or equivalent) entered a 4-week run-in period during which all subjects 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 was 341 (18.4) mL compared with 377 (18.5) mL for fluticasone propionate/salmeterol 250 mcg/50 mcg (treatment difference -37 mL; 95% CI: -88, 15; P = 0.162).

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

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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 (Medication Guide and Instructions for Use).

Asthma-Related Death

Inform patients with asthma that LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. **Also inform them that currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA.**

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.

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

Instruct patients not to use other LABA for COPD and asthma.

Local Effects

Inform patients that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with

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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.

Pneumonia

Patients with COPD have a higher risk of pneumonia; instruct them to contact their healthcare providers if they develop symptoms of pneumonia.

Immunosuppression

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.

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.

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.

Ocular Effects

Inform patients that long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); consider regular eye examinations.

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.

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.

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BREO ELLIPTA was developed in collaboration with Theravance.

GlaxoSmithKline
Research Triangle Park, NC 27709

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BRE:7PI

MEDICATION GUIDE

BREO® ELLIPTA® (*BREE-oh ee-LIP-ta)* 100/25
(fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder)

BREO® ELLIPTA® 200/25
(fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder)

What is the most important information I should know about BREO ELLIPTA?

BREO ELLIPTA can cause serious side effects, including:

- **People with asthma who take long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as vilanterol (one of the medicines in BREO ELLIPTA), have an increased risk of death from asthma problems.** It is not known whether fluticasone furoate, the other medicine in BREO ELLIPTA, reduces the risk of death from asthma problems seen with LABA medicines.
- **It is not known if LABA medicines, such as vilanterol, increase the risk of death in people with COPD.**
- **Call your healthcare provider if breathing problems worsen over time while using BREO ELLIPTA.** You may need different treatment.
- **Get emergency medical care if:**
  - your breathing problems worsen quickly
  - you use your rescue inhaler, but it does not relieve your breathing problems.
- For people with asthma, BREO ELLIPTA should be used only if your healthcare provider decides that your asthma is not well controlled with a long-term asthma control medicine, such as an inhaled corticosteroid. When your asthma is well controlled, your healthcare provider may tell you to stop taking BREO ELLIPTA. Your healthcare provider will decide if you can stop BREO ELLIPTA without loss of asthma control. Your healthcare provider may prescribe a different asthma control medicine for you, such as an inhaled corticosteroid.

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- Children and adolescents who take LABA medicines may have an increased risk of being hospitalized for asthma problems.

What is BREO ELLIPTA?

- BREO ELLIPTA combines an inhaled corticosteroid (ICS) medicine, fluticasone furoate, and a 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 should not be used in children and adolescents. It is not known if BREO ELLIPTA is safe and effective in children and adolescents younger than 18 years of age.
- BREO ELLIPTA is used for COPD and asthma as follows:

  COPD:

  BREO ELLIPTA 100/25 is a prescription medicine used to treat COPD. COPD is a chronic lung disease that includes chronic bronchitis, emphysema, or both. BREO ELLIPTA 100/25 is used long term as 1 inhalation 1 time each day 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).

  BREO ELLIPTA is not used to relieve sudden breathing problems and will not replace a rescue inhaler.

  Asthma:

  BREO ELLIPTA is a prescription medicine used as 1 inhalation 1 time each day 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 increase the risk of death from asthma problems.

  BREO ELLIPTA is not for people with asthma who are well controlled with an asthma control medicine, such as a low to medium dose of an inhaled corticosteroid medicine.

  BREO ELLIPTA is not used to relieve sudden breathing problems and will not replace a rescue inhaler.

Who should not use BREO ELLIPTA?

Do not use BREO ELLIPTA if you:

- have a severe allergy to milk proteins. Ask your healthcare provider if you are not sure.

- are allergic to fluticasone furoate, vilanterol, or any of the ingredients in BREO ELLIPTA. See “What are the ingredients in BREO ELLIPTA?” below for a complete list of ingredients.

What should I tell my healthcare provider before using BREO ELLIPTA?

Tell your healthcare provider about all of your health conditions, including if you:

- have heart problems.
- have high blood pressure.
- have seizures.
- have thyroid problems.
- have diabetes.
- have liver problems.
- have weak bones (osteoporosis).
- have an immune system problem.
- have eye problems such as glaucoma or cataracts.
- are allergic to any of the ingredients in BREO ELLIPTA, any other medicines, or food products. See “What are the ingredients in BREO ELLIPTA?” below for a complete list of ingredients.
- have any type of viral, bacterial, or fungal infection.
- are exposed to chickenpox or measles.
- have any other medical conditions.
- are pregnant or planning to become pregnant. It is not known if BREO ELLIPTA may harm your unborn baby.
- are breastfeeding. It is not known if the medicines in BREO ELLIPTA pass into your 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 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 Medication Guide.

- **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 2 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.
- 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 breathing problems.** 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.
  - you need to use 4 or more inhalations of your rescue inhaler in 24 hours for 2 or more days in a row.
  - you use 1 whole canister of your rescue inhaler in 8 weeks.
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - you have asthma and your symptoms do not improve after using BREO ELLIPTA regularly for 1 week.

What are the possible side effects with BREO ELLIPTA?

BREO ELLIPTA can cause serious side effects, including:

- **See “What is the most important information I should know about BREO ELLIPTA?”**

- **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 inhaled corticosteroid (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 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
- **sudden breathing problems immediately after inhaling your medicine.** If you have sudden breathing problems immediately after inhaling your medicine, stop taking 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)**
- **eye problems including glaucoma and cataracts.** You should have regular eye exams while using BREO ELLIPTA.
- **changes in laboratory blood values (sugar, potassium)**
- **slowed growth in children**

Common side effects of BREO ELLIPTA include:

COPD:
- runny nose and sore throat
- upper respiratory tract infection
- headache
- thrush in your mouth or throat. Rinse your mouth with water without swallowing after use to help prevent this.

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

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with BREO ELLIPTA. Ask your healthcare provider or pharmacist for more information.

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

How do 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 foil tray and only open when ready for use.
- Safely throw away BREO ELLIPTA in the trash 6 weeks after you open the foil 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 not mentioned in a Medication Guide. Do not use BREO ELLIPTA for a condition for which it was not prescribed. Do not give your BREO ELLIPTA to other people, even if they have the same condition that you have. It may harm them.

This Medication Guide summarizes the most important information about BREO ELLIPTA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about BREO ELLIPTA that was written for healthcare professionals.

For more information about BREO ELLIPTA, call 1-888-825-5249 or visit our website at www.myBREO.com.

What are the ingredients in BREO ELLIPTA?

Active ingredients: fluticasone furoate, vilanterol
Inactive ingredients: lactose monohydrate (contains milk proteins), magnesium stearate

This Medication Guide has been approved by the U.S. Food and Drug Administration.

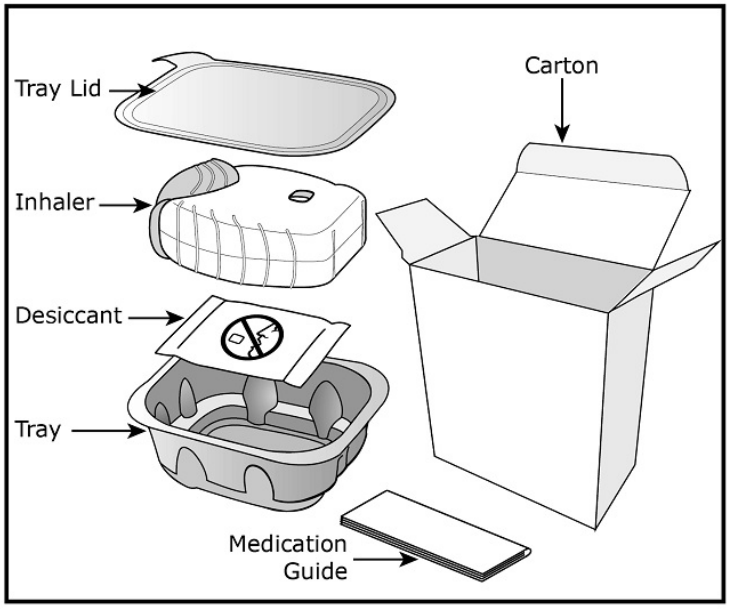
Instructions for Use

For Oral Inhalation Only.

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 foil 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.

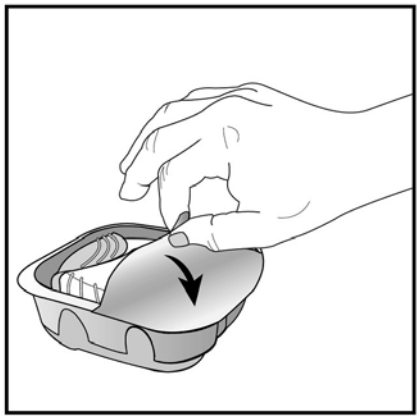


Figure A

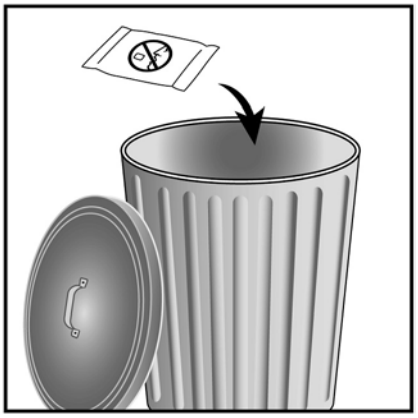


Figure B

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.

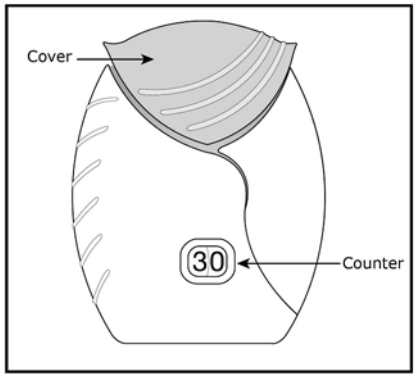


Figure C

- 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.

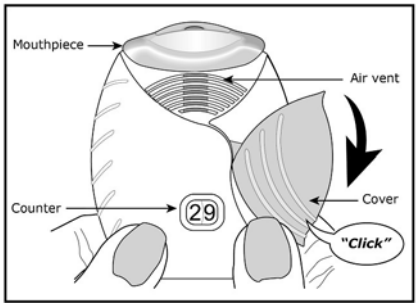


Figure D

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.

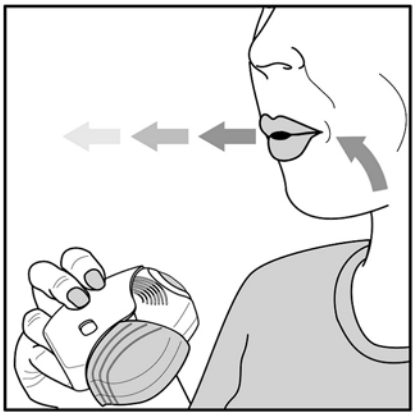


Figure E

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.

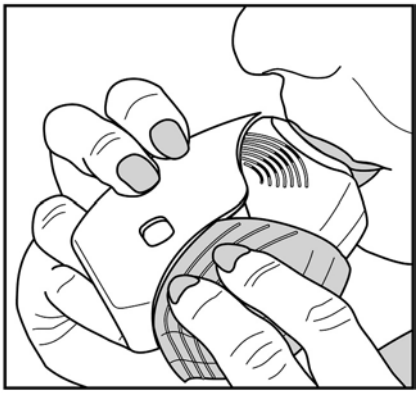


Figure F

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.**

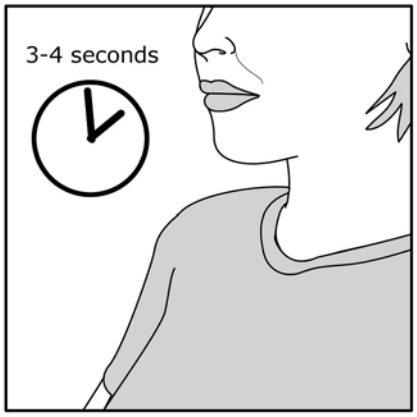


Figure H

- **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.**

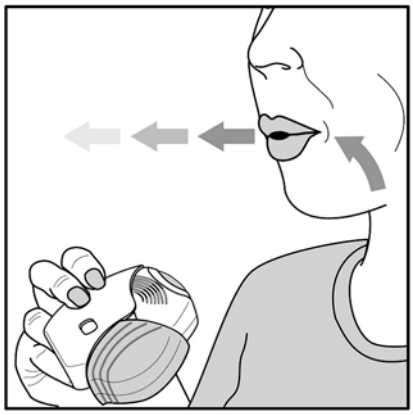


Figure I

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.

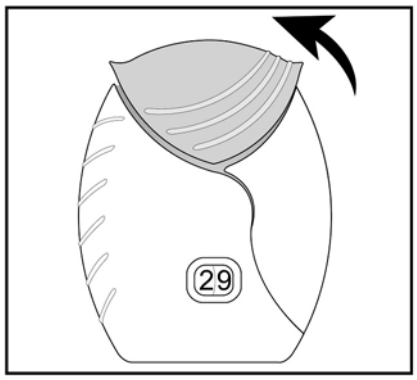


Figure J

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?

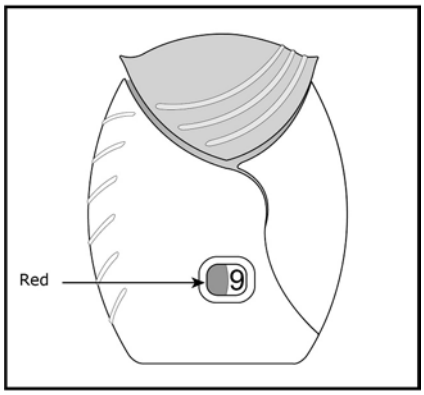


Figure L

- **When you have less 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.

If you have questions about BREO ELLIPTA or how to use your inhaler, call GlaxoSmithKline (GSK) at 1-888-825-5249 or visit www.myBREO.com.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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