

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder)
FOR ORAL INHALATION USE**
Initial U.S. Approval: 2013

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning.

- Long-acting beta₂-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the risk of asthma-related death. A placebo-controlled trial with another LABA (salmeterol) showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including vilanterol. (5.1)
- The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma. (5.1)

INDICATIONS AND USAGE

BREO ELLIPTA is a combination of fluticasone furoate, an inhaled corticosteroid (ICS), and vilanterol, a long-acting beta₂-adrenergic agonist (LABA), indicated for long-term, once-daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). (1)

Important limitations: Not indicated for relief of acute bronchospasm or for treatment of asthma. (1, 5.2)

DOSAGE AND ADMINISTRATION

- For oral inhalation only. (2)
- Maintenance treatment of COPD: 1 inhalation of BREO ELLIPTA 100 mcg/25 mcg once daily. (2)

DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Inhaler containing 2 double-foil blister strips of powder formulation for oral inhalation. One strip contains fluticasone furoate 100 mcg per blister and the other contains vilanterol 25 mcg per blister. (3)

CONTRAINDICATIONS

Severe hypersensitivity to milk proteins or any ingredients. (4)

WARNINGS AND PRECAUTIONS

- LABA increase the risk of asthma-related death. (5.1)
- Do not initiate in acutely deteriorating COPD or to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing 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 without swallowing after inhalation to help reduce the risk. (5.4)

- Increased risk of pneumonia in patients with COPD taking BREO ELLIPTA. Monitor patients for signs and symptoms of pneumonia. (5.5)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infection; 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

Most common adverse reactions (incidence $\geq 3\%$) are nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis. (6.1)

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.

Revised: 3/2015

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1 FULL PRESCRIBING INFORMATION

WARNING: asthma-related death

Long-acting beta₂-adrenergic agonists (LABA) 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, including vilanterol, an active ingredient in BREO[®] ELLIPTA[®] [see Warnings and Precautions (5.1)].

The safety and efficacy of BREO ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not indicated for the treatment of asthma.

1 INDICATIONS AND USAGE

BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta₂-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 is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

Important Limitations of Use: BREO ELLIPTA is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

2 DOSAGE AND ADMINISTRATION

BREO ELLIPTA 100 mcg/25 mcg should be administered as 1 inhalation once daily by the orally inhaled route only. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis.

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

No dosage adjustment is required for geriatric patients, patients with hepatic impairment, or renally impaired patients [see *Clinical Pharmacology* (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Inhalation Powder. Disposable light grey and pale blue plastic inhaler containing 2 double-foil blister strips, each with 30 blisters containing powder intended for oral inhalation only. One strip contains fluticasone furoate (100 mcg per blister), and the other strip contains

31 vilanterol (25 mcg per blister). An institutional pack containing 14 blisters per strip is also
32 available.

33 **4 CONTRAINDICATIONS**

34 The use of BREO ELLIPTA is contraindicated in patients with severe hypersensitivity to
35 milk proteins or who have demonstrated hypersensitivity to either fluticasone furoate, vilanterol,
36 or any of the excipients [see Warnings and Precautions (5.11), Description (11)].

37 **5 WARNINGS AND PRECAUTIONS**

38 **5.1 Asthma-Related Death**

- 39 • Data from a large placebo-controlled trial in subjects with asthma showed that LABA may
40 increase the risk of asthma-related death. Data are not available to determine whether the
41 rate of death in patients with COPD is increased by LABA.
- 42 • A 28-week, placebo-controlled, US trial comparing the safety of another LABA (salmeterol)
43 with placebo, each added to usual asthma therapy, showed an increase in asthma-related
44 deaths in subjects receiving salmeterol (13/13,176 in subjects treated with salmeterol vs
45 3/13,179 in subjects treated with placebo; relative risk: 4.37 [95% CI: 1.25, 15.34]). The
46 increased risk of asthma-related death is considered a class effect of LABA, including
47 vilanterol, one of the active ingredients in BREO ELLIPTA.
- 48 • No study adequate to determine whether the rate of asthma-related death is increased in
49 subjects treated with BREO ELLIPTA has been conducted. The safety and efficacy of BREO
50 ELLIPTA in patients with asthma have not been established. BREO ELLIPTA is not
51 indicated for the treatment of asthma.

52 **5.2 Deterioration of Disease and Acute Episodes**

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

57 BREO ELLIPTA should not be used for the relief of acute symptoms, i.e., as rescue
58 therapy for the treatment of acute episodes of bronchospasm. BREO ELLIPTA has not been
59 studied in the relief of acute symptoms and extra doses should not be used for that purpose.
60 Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist.

61 When beginning treatment with BREO ELLIPTA, patients who have been taking oral or
62 inhaled, short-acting beta₂-agonists on a regular basis (e.g., 4 times a day) should be instructed to
63 discontinue the regular use of these drugs and to use them only for symptomatic relief of acute
64 respiratory symptoms. When prescribing BREO ELLIPTA, the healthcare provider should also
65 prescribe an inhaled, short-acting beta₂-agonist and instruct the patient on how it should be used.
66 Increasing inhaled, short-acting beta₂-agonist use is a signal of deteriorating disease for which
67 prompt medical attention is indicated.

68 COPD may deteriorate acutely over a period of hours or chronically over several days or
69 longer. If BREO ELLIPTA no longer controls symptoms of bronchoconstriction; the patient's

70 inhaled, short-acting, beta₂-agonist becomes less effective; or the patient needs more short-acting
71 beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting a
72 re-evaluation of the patient and the COPD treatment regimen should be undertaken at once.
73 Increasing the daily dose of BREO ELLIPTA beyond the recommended dose is not appropriate
74 in this situation.

75 **5.3 Excessive Use of BREO ELLIPTA and Use With Other Long-Acting** 76 **Beta₂-Agonists**

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

83 **5.4 Local Effects of Inhaled Corticosteroids**

84 In clinical trials, the development of localized infections of the mouth and pharynx with
85 *Candida albicans* has occurred in subjects treated with BREO ELLIPTA. When such an
86 infection develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal
87 therapy while treatment with BREO ELLIPTA continues, but at times therapy with BREO
88 ELLIPTA may need to be interrupted. Advise the patient to rinse his/her mouth without
89 swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

90 **5.5 Pneumonia**

91 An increase in the incidence of pneumonia has been observed in subjects with COPD
92 receiving the fluticasone furoate/vilanterol combination, including BREO ELLIPTA
93 100 mcg/25 mcg, in clinical trials. There was also an increased incidence of pneumonias
94 resulting in hospitalization. In some incidences these pneumonia events were fatal. Physicians
95 should remain vigilant for the possible development of pneumonia in patients with COPD as the
96 clinical features of such infections overlap with the symptoms of COPD exacerbations.

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

106 **5.6 Immunosuppression**

107 Persons who are using drugs that suppress the immune system are more susceptible to
108 infections than healthy individuals. Chickenpox and measles, for example, can have a more
109 serious or even fatal course in susceptible children or adults using corticosteroids. In such

110 children or adults who have not had these diseases or been properly immunized, particular care
111 should be taken to avoid exposure. How the dose, route, and duration of corticosteroid
112 administration affect the risk of developing a disseminated infection is not known. The
113 contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not
114 known. If a patient is exposed to chickenpox, prophylaxis with varicella zoster immune globulin
115 (VZIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled
116 intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for
117 complete VZIG and IG prescribing information.) If chickenpox develops, treatment with
118 antiviral agents may be considered.

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

122 **5.7 Transferring Patients From Systemic Corticosteroid Therapy**

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

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

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

141 Patients requiring oral corticosteroids should be weaned slowly from systemic
142 corticosteroid use after transferring to BREO ELLIPTA. Prednisone reduction can be
143 accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during therapy
144 with BREO ELLIPTA. Lung function (mean forced expiratory volume in 1 second [FEV₁]),
145 beta-agonist use, and COPD symptoms should be carefully monitored during withdrawal of oral
146 corticosteroids. In addition, patients should be observed for signs and symptoms of adrenal
147 insufficiency, such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

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

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

154 **5.8 Hypercorticism and Adrenal Suppression**

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

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

164 It is possible that systemic corticosteroid effects such as hypercorticism and adrenal
165 suppression (including adrenal crisis) may appear in a small number of patients who are sensitive
166 to these effects. If such effects occur, BREO ELLIPTA should be reduced slowly, consistent
167 with accepted procedures for reducing systemic corticosteroids, and other treatments for
168 management of COPD symptoms should be considered.

169 **5.9 Drug Interactions With Strong Cytochrome P450 3A4 Inhibitors**

170 Caution should be exercised when considering the coadministration of BREO ELLIPTA
171 with long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir,
172 clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir,
173 telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and
174 increased cardiovascular adverse effects may occur [*see Drug Interactions (7.1), Clinical*
175 *Pharmacology (12.3)*].

176 **5.10 Paradoxical Bronchospasm**

177 As with other inhaled medicines, BREO ELLIPTA can produce paradoxical
178 bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following
179 dosing with BREO ELLIPTA, it should be treated immediately with an inhaled, short-acting
180 bronchodilator; BREO ELLIPTA should be discontinued immediately; and alternative therapy
181 should be instituted.

182 **5.11 Hypersensitivity Reactions, Including Anaphylaxis**

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

188 **5.12 Cardiovascular Effects**

189 Vilanterol, like other beta₂-agonists, can produce a clinically significant cardiovascular
190 effect in some patients as measured by increases in pulse rate, systolic or diastolic blood
191 pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. If
192 such effects occur, BREO ELLIPTA may need to be discontinued. In addition, beta-agonists
193 have been reported to produce electrocardiographic changes, such as flattening of the T wave,
194 prolongation of the QTc interval, and ST segment depression, although the clinical significance
195 of these findings is unknown. In healthy subjects, large doses of inhaled fluticasone
196 furoate/vilanterol (4 times the recommended dose of vilanterol, representing a 12-fold higher
197 systemic exposure than seen in patients with COPD) have been associated with clinically
198 significant prolongation of the QTc interval, which has the potential for producing ventricular
199 arrhythmias. Therefore, BREO ELLIPTA, like other sympathomimetic amines, should be used
200 with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac
201 arrhythmias, and hypertension.

202 **5.13 Reduction in Bone Mineral Density**

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

214 In replicate 12-month trials in 3,255 subjects with COPD, bone fractures were reported
215 by 2% of subjects receiving the fluticasone furoate/vilanterol combination (50 mcg/25 mcg: 2%
216 [14 of 820 subjects]; 100 mcg/25 mcg: 2% [19 of 806 subjects]; or 200 mcg/25 mcg: 2% [14 of
217 811 subjects]) than in subjects receiving vilanterol 25 mcg alone (less than 1% [8 of 818
218 subjects]).

219 **5.14 Glaucoma and Cataracts**

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

224 In replicate 12-month trials in 3,255 subjects with COPD, similar incidences of ocular
225 effects (including glaucoma and cataracts) were reported in subjects receiving the fluticasone
226 furoate/vilanterol combination (50 mcg/25 mcg: less than 1% [7 of 820 subjects]; 100 mcg/25

227 mcg: 1% [12 of 806 subjects]; 200 mcg/25 mcg: less than 1% [7 of 811 subjects]) as those
228 receiving vilanterol 25 mcg alone (1% [9 of 818 subjects]).

229 **5.15 Coexisting Conditions**

230 BREO ELLIPTA, like all medicines containing sympathomimetic amines, should be used
231 with caution in patients with convulsive disorders or thyrotoxicosis and in those who are
232 unusually responsive to sympathomimetic amines. Doses of the related beta₂-adrenoceptor
233 agonist albuterol, when administered intravenously, have been reported to aggravate preexisting
234 diabetes mellitus and ketoacidosis.

235 **5.16 Hypokalemia and Hyperglycemia**

236 Beta-adrenergic agonist medicines may produce significant hypokalemia in some
237 patients, possibly through intracellular shunting, which has the potential to produce adverse
238 cardiovascular effects. The decrease in serum potassium is usually transient, not requiring
239 supplementation. Beta-agonist medications may produce transient hyperglycemia in some
240 patients. In 4 clinical trials of 6- and 12-month duration evaluating BREO ELLIPTA in subjects
241 with COPD, there was no evidence of a treatment effect on serum glucose or potassium.

242 **6 ADVERSE REACTIONS**

243 LABA, such as vilanterol, one of the active ingredients in BREO ELLIPTA, increase the
244 risk of asthma-related death. BREO ELLIPTA is not indicated for the treatment of asthma. [See
245 *Boxed Warnings and Warnings and Precautions (5.1).*]

246 Systemic and local corticosteroid use may result in the following:

- 247 • Increased risk of pneumonia in COPD [see *Warnings and Precautions (5.5)*]
- 248 • Increased risk for decrease in bone mineral density [see *Warnings and Precautions (5.13)*]

249 **6.1 Clinical Trials Experience**

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

253 The clinical program for BREO ELLIPTA included 7,700 subjects with COPD in two
254 6-month lung function trials, two 12-month exacerbation trials, and 6 other trials of shorter
255 duration. A total of 2,034 subjects have received at least 1 dose of BREO ELLIPTA 100 mcg/25
256 mcg, and 1,087 subjects have received higher doses of fluticasone furoate/vilanterol. The safety
257 data described below are based on the confirmatory 6-month and 12-month trials. Adverse
258 reactions observed in the other trials were similar to those observed in the confirmatory trials.

259 **6-Month Trials:** The incidence of adverse reactions associated with BREO ELLIPTA in
260 Table 1 is based on 2 placebo-controlled, 6-month clinical trials (Trials 1 and 2; n = 1,224 and
261 n = 1,030, respectively). Of the 2,254 subjects, 70% were male and 84% were Caucasian. They
262 had a mean age of 62 years and an average smoking history of 44 pack years, with 54%
263 identified as current smokers. At screening, the mean postbronchodilator percent predicted FEV₁
264 was 48% (range: 14% to 87%), the mean postbronchodilator FEV₁/forced vital capacity (FVC)

265 ratio was 47% (range: 17% to 88%), and the mean percent reversibility was 14% (range: -41% to
266 152%).

267 Subjects received 1 inhalation once daily of the following: BREO ELLIPTA
268 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol
269 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate 200 mcg, vilanterol 25 mcg, or
270 placebo.

271

272 **Table 1. Adverse Reactions With $\geq 3\%$ Incidence and More Common Than Placebo With**
273 **BREO ELLIPTA in Subjects With Chronic Obstructive Pulmonary Disease**

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

274 ^a Includes terms oral candidiasis, oropharyngeal candidiasis, candidiasis, and oropharyngitis
275 fungal.

276

277 **12-Month Trials:** Long-term safety data is based on two 12-month trials (Trials 3 and 4;
278 n = 1,633 and n = 1,622, respectively). Trials 3 and 4 included 3,255 subjects, of which 57%
279 were male and 85% were Caucasian. They had a mean age of 64 years and an average smoking
280 history of 46 pack years, with 44% identified as current smokers. At screening, the mean
281 postbronchodilator percent predicted FEV₁ was 45% (range: 12% to 91%), and the mean
282 postbronchodilator FEV₁/FVC ratio was 46% (range: 17% to 81%), indicating that the subject
283 population had moderate to very severely impaired airflow obstruction. Subjects received 1
284 inhalation once daily of the following: BREO ELLIPTA 100 mcg/25 mcg, fluticasone
285 furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate/vilanterol 200 mcg/25 mcg, or vilanterol
286 25 mcg. In addition to the events shown in Table 1, adverse reactions occurring in greater than or
287 equal to 3% of the subjects treated with BREO ELLIPTA (N = 806) for 12 months included
288 COPD, back pain, pneumonia [see *Warnings and Precautions (5.5)*], bronchitis, sinusitis, cough,

289 oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, diarrhea, peripheral edema,
290 and pyrexia.

291 **6.2 Postmarketing Experience**

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

298 Immune System Disorders: Hypersensitivity reactions including anaphylaxis,
299 angioedema, rash, and urticaria.

300 **7 DRUG INTERACTIONS**

301 **7.1 Inhibitors of Cytochrome P450 3A4**

302 Fluticasone furoate and vilanterol, the individual components of BREO ELLIPTA, are
303 both substrates of CYP3A4. Concomitant administration of the potent CYP3A4 inhibitor
304 ketoconazole increases the systemic exposure to fluticasone furoate and vilanterol. Caution
305 should be exercised when considering the coadministration of BREO ELLIPTA with long-term
306 ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin,
307 conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin,
308 troleandomycin, voriconazole) [*see Warnings and Precautions (5.9) and Clinical Pharmacology*
309 (*12.3*)].

310 **7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants**

311 Vilanterol, like other beta₂-agonists, should be administered with extreme caution to
312 patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs
313 known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because
314 the effect of adrenergic agonists on the cardiovascular system may be potentiated by these
315 agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular
316 arrhythmias.

317 **7.3 Beta-Adrenergic Receptor Blocking Agents**

318 Beta-blockers not only block the pulmonary effect of beta-agonists, such as vilanterol, a
319 component of BREO ELLIPTA, but may produce severe bronchospasm in patients with
320 reversible obstructive airways disease. Therefore, patients with COPD should not normally be
321 treated with beta-blockers. However, under certain circumstances, there may be no acceptable
322 alternatives to the use of beta-adrenergic blocking agents for these patients; cardioselective beta-
323 blockers could be considered, although they should be administered with caution.

324 **7.4 Non-Potassium-Sparing Diuretics**

325 The electrocardiographic changes and/or hypokalemia that may result from the
326 administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be
327 acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is

328 exceeded. Although the clinical significance of these effects is not known, caution is advised in
329 the coadministration of beta-agonists with non-potassium-sparing diuretics.

330 **8 USE IN SPECIFIC POPULATIONS**

331 **8.1 Pregnancy**

332 Teratogenic Effects: Pregnancy Category C. There are no adequate and well-controlled
333 trials with BREO ELLIPTA in pregnant women. Corticosteroids and beta₂-agonists have been
334 shown to be teratogenic in laboratory animals when administered systemically at relatively low
335 dosage levels. Because animal studies are not always predictive of human response, BREO
336 ELLIPTA should be used during pregnancy only if the potential benefit justifies the potential
337 risk to the fetus. Women should be advised to contact their physicians if they become pregnant
338 while taking BREO ELLIPTA.

339 *Fluticasone Furoate and Vilanterol:* There was no evidence of teratogenic
340 interactions between fluticasone furoate and vilanterol in rats at approximately 9 and 40 times,
341 respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on
342 a mcg/m² basis at maternal inhaled doses of fluticasone furoate and vilanterol, alone or in
343 combination, up to approximately 95 mcg/kg/day).

344 *Fluticasone Furoate:* There were no teratogenic effects in rats and rabbits at
345 approximately 9 and 2 times, respectively, the MRHDID in adults (on a mcg/m² basis at
346 maternal inhaled doses up to 91 and 8 mcg/kg/day in rats and rabbits, respectively). There were
347 no effects on perinatal and postnatal development in rats at approximately 3 times the MRHDID
348 in adults (on a mcg/m² basis at maternal doses up to 27 mcg/kg/day).

349 *Vilanterol:* There were no teratogenic effects in rats and rabbits at approximately
350 13,000 and 160 times, respectively, the MRHDID in adults (on a mcg/m² basis at maternal
351 inhaled doses up to 33,700 mcg/kg/day in rats and on an AUC basis at maternal inhaled doses up
352 to 591 mcg/kg/day in rabbits). However, fetal skeletal variations were observed in rabbits at
353 approximately 1,000 times the MRHDID in adults (on an AUC basis at maternal inhaled or
354 subcutaneous doses of 5,740 or 300 mcg/kg/day, respectively). The skeletal variations included
355 decreased or absent ossification in cervical vertebral centrum and metacarpals. There were no
356 effects on perinatal and postnatal development in rats at approximately 3,900 times the
357 MRHDID in adults (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

358 Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers
359 receiving corticosteroids during pregnancy. Such infants should be carefully monitored.

360 **8.2 Labor and Delivery**

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

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

365 **8.3 Nursing Mothers**

366 It is not known whether fluticasone furoate or vilanterol are excreted in human breast
367 milk. However, other corticosteroids and beta₂-agonists have been detected in human milk. Since
368 there are no data from controlled trials on the use of BREO ELLIPTA by nursing mothers,
369 caution should be exercised when it is administered to a nursing woman.

370 **8.4 Pediatric Use**

371 BREO ELLIPTA is not indicated for use in children. The safety and efficacy in pediatric
372 patients have not been established.

373 **8.5 Geriatric Use**

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

376 Clinical trials of BREO ELLIPTA for COPD included 2,508 subjects aged 65 and older
377 and 564 subjects aged 75 and older. No overall differences in safety or effectiveness were
378 observed between these subjects and younger subjects, and other reported clinical experience has
379 not identified differences in responses between the elderly and younger subjects.

380 **8.6 Hepatic Impairment**

381 Fluticasone furoate systemic exposure increased by up to 3-fold in subjects with hepatic
382 impairment compared with healthy subjects. Hepatic impairment had no effect on vilanterol
383 systemic exposure. Use BREO ELLIPTA with caution in patients with moderate or severe
384 hepatic impairment. Monitor patients for corticosteroid-related side effects [*see Clinical*
385 *Pharmacology (12.3)*].

386 **8.7 Renal Impairment**

387 There were no significant increases in either fluticasone furoate or vilanterol exposure in
388 subjects with severe renal impairment (CrCl<30 mL/min) compared with healthy subjects. No
389 dosage adjustment is required in patients with renal impairment [*see Clinical Pharmacology*
390 *(12.3)*].

391 **10 OVERDOSAGE**

392 No human overdosage data has been reported for BREO ELLIPTA.

393 BREO ELLIPTA contains both fluticasone furoate and vilanterol; therefore, the risks
394 associated with overdosage for the individual components described below apply to BREO
395 ELLIPTA.

396 **10.1 Fluticasone Furoate**

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

401 Single- and repeat-dose trials of fluticasone furoate at doses of 50 to 4,000 mcg have
402 been studied in human subjects. Decreases in mean serum cortisol were observed at dosages of
403 500 mcg or higher given once daily for 14 days.

404 **10.2 Vilanterol**

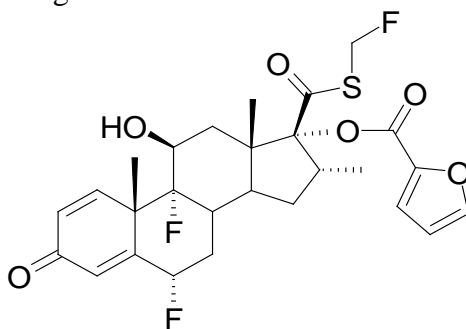
405 The expected signs and symptoms with overdosage of vilanterol are those of excessive
406 beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms
407 of beta-adrenergic stimulation (e.g., angina, hypertension or hypotension, tachycardia with rates
408 up to 200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

412 Treatment of overdosage consists of discontinuation of BREO ELLIPTA together with
413 institution of appropriate symptomatic and/or supportive therapy. The judicious use of a
414 cardioselective beta-receptor blocker may be considered, bearing in mind that such medicine can
415 produce bronchospasm. Cardiac monitoring is recommended in cases of overdosage.

416 11 DESCRIPTION

417 BREO ELLIPTA is a combination of fluticasone furoate (an ICS) and vilanterol (a
418 LABA).

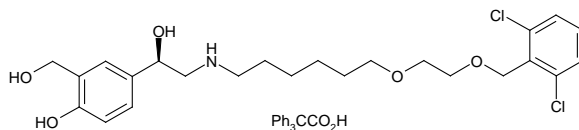
419 One active component of BREO ELLIPTA is fluticasone furoate, a synthetic
420 trifluorinated corticosteroid having the chemical name (6 α ,11 β ,16 α ,17 α)-6,9-difluoro-17-
421 {[(fluoro-methyl)thio]carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl 2-
422 furancarboxylate and the following chemical structure:



423

424 Fluticasone furoate is a white powder with a molecular weight of 538.6, and the empirical
425 formula is C₂₇H₂₉F₃O₆S. It is practically insoluble in water.

426 The other active component of BREO ELLIPTA is vilanterol trifenate, a LABA with
427 the chemical name triphenylacetic acid-4-{(1R)-2-[(6-{2-[2,6-dichlorobenzyl]oxy}ethoxy)
428 hexyl]amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol (1:1) and the following chemical
429 structure:



430

431 Vilanterol trifenate is a white powder with a molecular weight of 774.8, and the
432 empirical formula is C₂₄H₃₃Cl₂NO₅•C₂₀H₁₆O₂. It is practically insoluble in water.

433 BREO ELLIPTA is a light grey and pale blue plastic inhaler containing 2 double-foil
434 blister strips. Each blister on one strip contains a white powder mix of micronized fluticasone

435 furoate (100 mcg) and lactose monohydrate (12.4 mg), and each blister on the other strip
436 contains a white powder mix of micronized vilanterol trifenate (40 mcg equivalent to 25 mcg
437 of vilanterol), magnesium stearate (125 mcg), and lactose monohydrate (12.34 mg). The lactose
438 monohydrate contains milk proteins. After the inhaler is activated, the powder within both
439 blisters is exposed and ready for dispersion into the airstream created by the patient inhaling
440 through the mouthpiece.

441 Under standardized in vitro test conditions, BREO ELLIPTA delivers 92 mcg of
442 fluticasone furoate and 22 mcg of vilanterol per blister when tested at a flow rate of 60 L/min for
443 4 seconds.

444 In adult subjects with obstructive lung disease and severely compromised lung function
445 (COPD with FEV₁/FVC less than 70% and FEV₁ less than 30% predicted or FEV₁ less than 50%
446 predicted plus chronic respiratory failure), mean peak inspiratory flow through the ELLIPTA
447 inhaler was 66.5 L/min (range: 43.5 to 81.0 L/min).

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

450 **12 CLINICAL PHARMACOLOGY**

451 **12.1 Mechanism of Action**

452 BREO ELLIPTA: Since BREO ELLIPTA contains both fluticasone furoate and
453 vilanterol, the mechanisms of action described below for the individual components apply to
454 BREO ELLIPTA. These drugs represent 2 different classes of medications (a synthetic
455 corticosteroid and a LABA) that have different effects on clinical and physiological indices.

456 Fluticasone Furoate: Fluticasone furoate is a synthetic trifluorinated corticosteroid with
457 anti-inflammatory activity. Fluticasone furoate has been shown in vitro to exhibit a binding
458 affinity for the human glucocorticoid receptor that is approximately 29.9 times that of
459 dexamethasone and 1.7 times that of fluticasone propionate. The clinical relevance of these in
460 vitro findings is unknown. The precise mechanism through which fluticasone furoate affects
461 COPD symptoms is not known. Corticosteroids have been shown to have a wide range of actions
462 on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and
463 mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation.
464 Specific effects of fluticasone furoate demonstrated in in vitro and in vivo models included
465 activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription
466 factors such as NFκB, and inhibition of antigen-induced lung eosinophilia in sensitized rats.

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

469 Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth
470 muscle and beta₁-receptors are the predominant receptors in the heart, there are also
471 beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors.
472 The precise function of these receptors has not been established, but they raise the possibility that
473 even highly selective beta₂-agonists may have cardiac effects.

474 The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including vilanterol, are
475 at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that
476 catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine
477 monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial
478 smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells,
479 especially from mast cells.

480 **12.2 Pharmacodynamics**

481 Cardiovascular Effects: Healthy Subjects: QTc interval prolongation was studied in a
482 double-blind, multiple dose, placebo- and positive-controlled crossover study in 85 healthy
483 volunteers. The maximum mean (95% upper confidence bound) difference in QTcF from
484 placebo after baseline-correction was 4.9 (7.5) milliseconds and 9.6 (12.2) milliseconds seen
485 30 minutes after dosing for fluticasone furoate /vilanterol 200mcg/25 mcg and fluticasone
486 furoate/vilanterol 800 mcg/100 mcg, respectively.

487 A dose-dependent increase in heart rate was also observed. The maximum mean (95%
488 upper confidence bound) difference in heart rate from placebo after baseline-correction was
489 7.8 (9.4) beats/min and 17.1 (18.7) beats/min seen 10 minutes after dosing for fluticasone
490 furoate/vilanterol 200 mcg/25 mcg and fluticasone furoate/vilanterol 800 mcg/100 mcg,
491 respectively.

492 Chronic Obstructive Pulmonary Disease: In 4 clinical trials of 6- and 12-month
493 duration, there was no evidence of a treatment effect on heart rate, QTcF, or blood pressure in
494 subjects with COPD given combination doses of fluticasone furoate (50, 100, or
495 200 mcg)/vilanterol 25 mcg, the individual components of fluticasone furoate or vilanterol alone,
496 or placebo [see *Clinical Studies (14)*].

497 HPA Axis Effects: Healthy Subjects: Inhaled fluticasone furoate at repeat doses up to
498 400 mcg was not associated with statistically significant decreases in serum or urinary cortisol in
499 healthy subjects. Decreases in serum and urine cortisol levels were observed at fluticasone
500 furoate exposures several-fold higher than exposures observed at the therapeutic dose.

501 Chronic Obstructive Pulmonary Disease: In a trial with subjects with COPD,
502 treatment with fluticasone furoate/vilanterol (50 mcg/25 mcg, 100 mcg/25 mcg, and
503 200 mcg/25 mcg), vilanterol 25 mcg, and fluticasone furoate (100 and 200 mcg) for 6 months did
504 not affect 24-hour urinary cortisol excretion. A separate trial with subjects with COPD
505 demonstrated no effects on serum cortisol after 28 days of treatment with fluticasone
506 furoate/vilanterol (50 mcg/25 mcg, 100 mcg/25 mcg, and 200 mcg/25 mcg).

507 **12.3 Pharmacokinetics**

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

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

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

526 Distribution: Fluticasone Furoate: Following intravenous administration to healthy
527 subjects, the mean volume of distribution at steady state was 661 L. Binding of fluticasone
528 furoate to human plasma proteins was high (99.6%).

529 Vilanterol: Following intravenous administration to healthy subjects, the mean
530 volume of distribution at steady state was 165 L. Binding of vilanterol to human plasma proteins
531 was 93.9%.

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

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

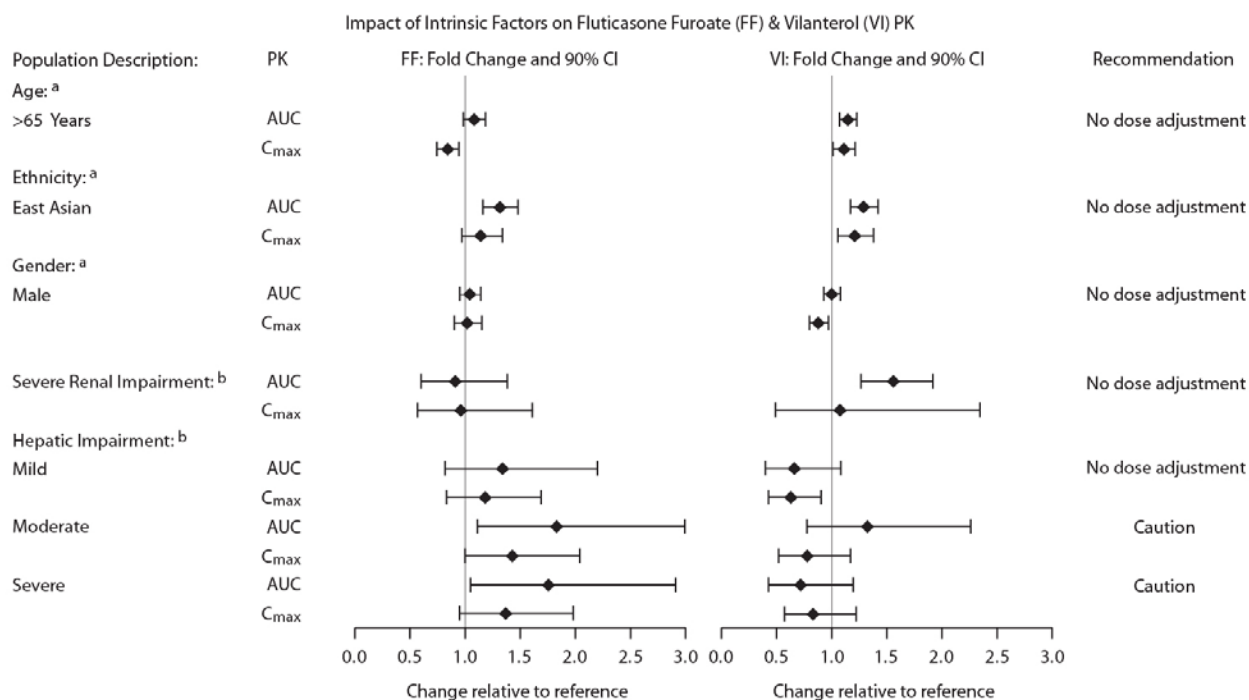
538 Elimination: Fluticasone Furoate: Fluticasone furoate and its metabolites are
539 eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and
540 intravenously administered dose, respectively. Urinary excretion accounted for approximately
541 1% and 2% of the orally and intravenously administered doses, respectively. Following repeat-
542 dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

543 Vilanterol: Following oral administration, vilanterol was eliminated mainly by
544 metabolism followed by excretion of metabolites in urine and feces (approximately 70% and
545 30% of the recovered radioactive dose, respectively). The effective half-life for accumulation of
546 vilanterol, as determined from inhalation administration of multiple doses of vilanterol 25 mcg,
547 is 21.3 hours in subjects with COPD.

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

550

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



553

554 ^a Age, gender, and ethnicity comparison for BREO ELLIPTA (fluticasone furoate/vilanterol
555 100 mcg/25 mcg) in subjects with COPD.

556 ^b Renal groups (fluticasone furoate/vilanterol 200 mcg/25 mcg) and hepatic groups (fluticasone
557 furoate/vilanterol 200 mcg/25 mcg or fluticasone furoate/vilanterol 100 mcg/12.5 mcg)
558 compared with healthy control group.

559

560 **Race:** Systemic exposure ($AUC_{(0-24)}$) to inhaled fluticasone furoate 200 mcg was 27%
561 to 49% higher in healthy subjects of Japanese, Korean, and Chinese heritage compared with
562 Caucasian subjects. Similar differences were observed for subjects with COPD (Figure 1).
563 However, there is no evidence that this higher exposure to fluticasone furoate results in clinically
564 relevant effects on urinary cortisol excretion or on efficacy in these racial groups.

565 There was no effect of race on the pharmacokinetics of vilanterol in subjects with COPD.

566 **Hepatic Impairment: Fluticasone Furoate:** Following repeat dosing of fluticasone
567 furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for
568 7 days, there was an increase of 34%, 83%, and 75% in fluticasone furoate systemic exposure
569 (AUC) in subjects with mild, moderate, and severe hepatic impairment, respectively, compared
570 with healthy subjects (see Figure 1).

571 In subjects with moderate hepatic impairment receiving fluticasone furoate/vilanterol
572 200 mcg/25 mcg, mean serum cortisol (0 to 24 hours) was reduced by 34% (95% CI: 11%, 51%)
573 compared with healthy subjects. In subjects with severe hepatic impairment receiving fluticasone
574 furoate/vilanterol 100 mcg/12.5 mcg, mean serum cortisol (0 to 24 hours) was increased by 14%

575 (95% CI: -16%, 55%) compared with healthy subjects. Patients with moderate to severe hepatic
576 disease should be closely monitored.

577 *Vilanterol:* Hepatic impairment had no effect on vilanterol systemic exposure
578 (C_{max} and $AUC_{(0-24)}$ on Day 7) following repeat-dose administration of fluticasone
579 furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for
580 7 days (see Figure 1).

581 There were no additional clinically relevant effects of the fluticasone furoate/vilanterol
582 combinations on heart rate or serum potassium in subjects with mild or moderate hepatic
583 impairment (vilanterol 25 mcg combination) or with severe hepatic impairment (vilanterol
584 12.5 mcg combination) compared with healthy subjects.

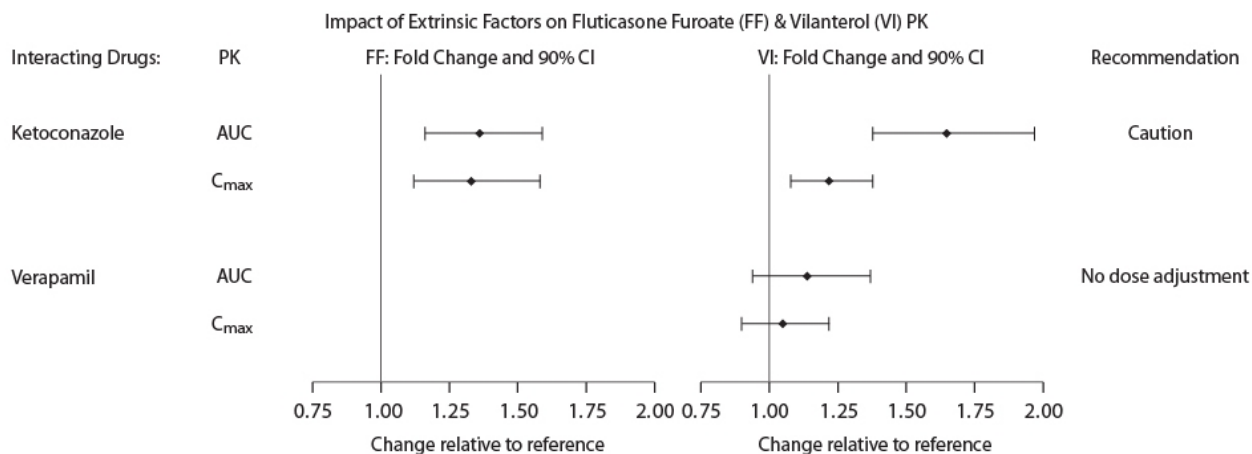
585 *Renal Impairment:* Fluticasone furoate systemic exposure was not increased and
586 vilanterol systemic exposure ($AUC_{(0-24)}$) was 56% higher in subjects with severe renal
587 impairment compared with healthy subjects (see Figure 1). There was no evidence of greater
588 corticosteroid or beta-agonist class-related systemic effects (assessed by serum cortisol, heart
589 rate, and serum potassium) in subjects with severe renal impairment compared with healthy
590 subjects.

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

596 *Inhibitors of Cytochrome P450 3A4:* The exposure (AUC) of fluticasone furoate
597 and vilanterol were 36% and 65% higher, respectively, when coadministered with ketoconazole
598 400 mg compared with placebo (see Figure 2). The increase in fluticasone furoate exposure was
599 associated with a 27% reduction in weighted mean serum cortisol (0 to 24 hours). The increase
600 in vilanterol exposure was not associated with an increase in beta-agonist-related systemic
601 effects on heart rate or blood potassium.

602

603 **Figure 2. Impact of Coadministered Drugs^a on the Pharmacokinetics (PK) of Fluticasone**
 604 **Furoate and Vilanterol Following Administration as Fluticasone Furoate/Vilanterol**
 605 **Combination or Vilanterol Coadministered With a Long-Acting Muscarinic Antagonist**



606
 607 ^a Compared with placebo group.

608
 609 *Inhibitors of P-glycoprotein:* Fluticasone furoate and vilanterol are both
 610 substrates of P-glycoprotein (P-gp). Coadministration of repeat-dose (240 mg once daily)
 611 verapamil (a potent P-gp inhibitor and moderate CYP3A4 inhibitor) did not affect the vilanterol
 612 C_{max} or AUC in healthy subjects (see Figure 2). Drug interaction trials with a specific P-gp
 613 inhibitor and fluticasone furoate have not been conducted.

614 13 NONCLINICAL TOXICOLOGY

615 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

619 **Fluticasone Furoate:** Fluticasone furoate produced no treatment-related increases in the
 620 incidence of tumors in 2-year inhalation studies in rats and mice at inhaled doses up to 9 and
 621 19 mcg/kg/day, respectively (approximately equal to the MRHDID in adults on a mcg/m² basis).

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

625 No evidence of impairment of fertility was observed in male and female rats at inhaled
 626 fluticasone furoate doses up to 29 and 91 mcg/kg/day, respectively (approximately 3 and 9 times,
 627 respectively, the MRHDID in adults on a mcg/m² basis).

628 **Vilanterol:** In a 2-year carcinogenicity study in mice, vilanterol caused a statistically
 629 significant increase in ovarian tubulostromal adenomas in females at an inhalation dose of
 630 29,500 mcg/kg/day (approximately 8,750 times the MRHDID in adults on an AUC basis). No

631 increase in tumors was seen at an inhalation dose of 615 mcg/kg/day (approximately 530 times
632 the MRHDID in adults on an AUC basis).

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

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

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

645 No evidence of impairment of fertility was observed in reproductive studies conducted in
646 male and female rats at inhaled vilanterol doses up to 31,500 and 37,100 mcg/kg/day,
647 respectively (approximately 12,000 and 14,000 times, respectively, the MRHDID in adults on a
648 mcg/m² basis).

649 **14 CLINICAL STUDIES**

650 The safety and efficacy of BREO ELLIPTA were evaluated in 7,700 subjects with
651 COPD. The development program included 4 confirmatory trials of 6- and 12-months' duration,
652 three 12-week active comparator trials, and dose-ranging trials of shorter duration. The efficacy
653 of BREO ELLIPTA is based primarily on the dose-ranging trials and the 4 confirmatory trials
654 described below.

655 **14.1 Dose-Ranging Trials**

656 Dose selection for BREO ELLIPTA for COPD was based on dose-ranging trials for the
657 individual components, vilanterol and fluticasone furoate, in patients with COPD and asthma.

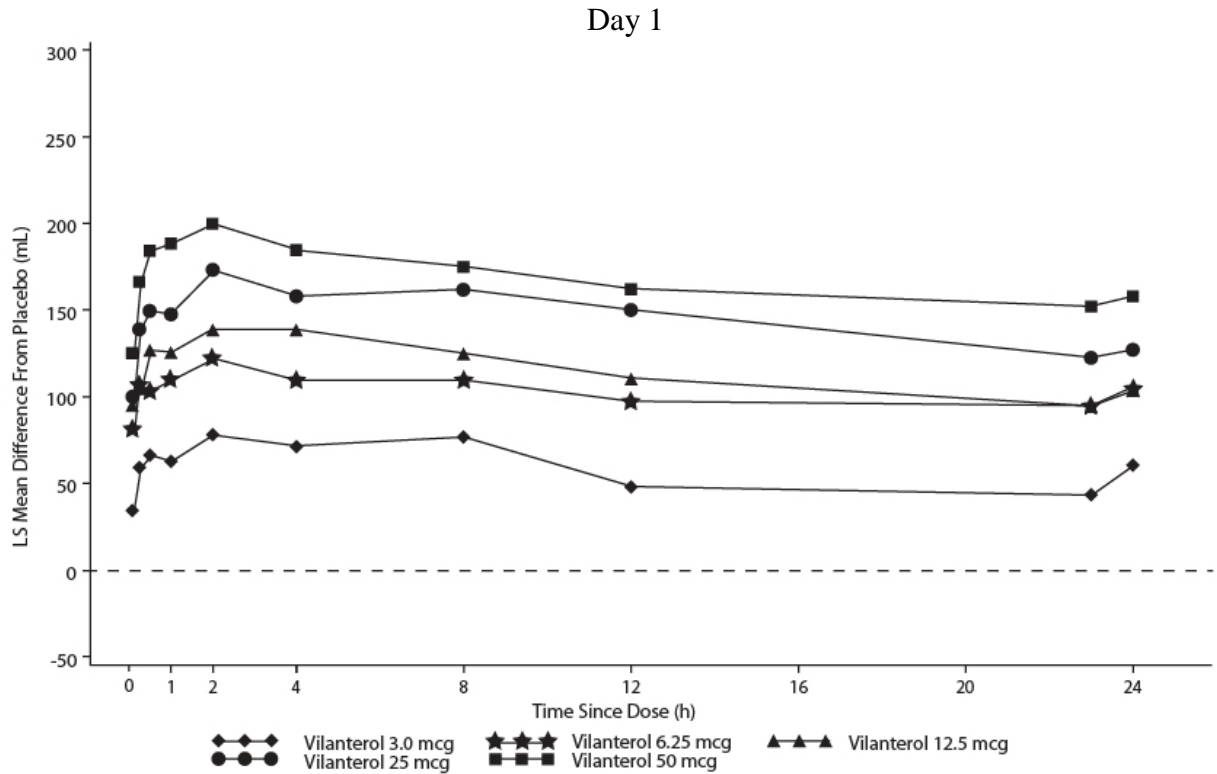
658 **BREO ELLIPTA 100 mcg/25 mcg is not indicated for asthma.**

659 Vilanterol: Dose selection for vilanterol in COPD was supported by a 28-day,
660 randomized, double-blind, placebo-controlled, parallel-group trial evaluating 5 doses of
661 vilanterol (3 to 50 mcg) or placebo dosed in the morning in 602 patients with COPD. Results
662 demonstrated dose-related increases in FEV₁ compared with placebo at Day 1 and Day 28
663 (Figure 3).

664

665 **Figure 3. Least Squares (LS) Mean Difference From Placebo in Post-Dose Serial FEV₁ (0-**
666 **24 h, mL) on Days 1 and 28**

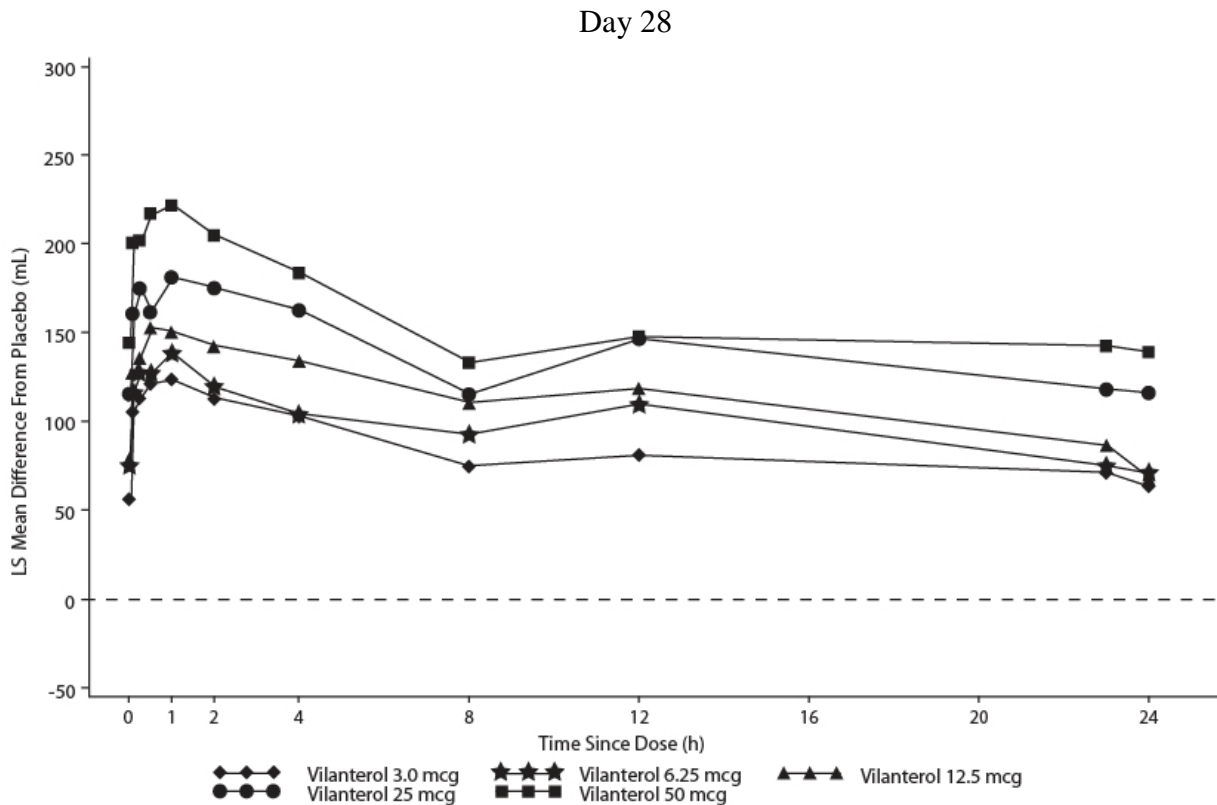
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672

673 The differences in trough FEV₁ on Day 28 from placebo for the 3-, 6.25-, 12.5-, 25-, and
674 50-mcg doses were 92 mL (95% CI: 39, 144), 98 mL (95% CI: 46, 150), 110 mL (95% CI: 57,
675 162), 137 mL (95% CI: 85, 190), and 165 mL (95% CI: 112, 217), respectively. These results
676 supported the evaluation of vilanterol 25 mcg in the confirmatory COPD trials.

677 Dose-ranging trials in subjects with asthma evaluated doses from 3 to 50 mcg and
678 12.5 mcg once-daily versus 6.25 mcg twice-daily dosing frequency. The results supported the
679 selection of the vilanterol 25 mcg once-daily dose for further evaluation in the confirmatory
680 COPD trials.

681 **Fluticasone Furoate:** Eight doses of fluticasone furoate ranging from 25 to 800 mcg
682 once daily were evaluated in 3 randomized, double-blind, placebo-controlled, 8-week trials in
683 subjects with asthma. A dose-related increase in trough FEV₁ at Week 8 was seen for doses from
684 25 to 200 mcg with no consistent additional benefit for doses above 200 mcg. To evaluate dosing
685 frequency, a separate trial compared fluticasone furoate 200 mcg once-daily, fluticasone furoate
686 100 mcg twice-daily, fluticasone propionate 100 mcg twice-daily, and fluticasone propionate
687 200 mcg once-daily. The results supported the selection of the once-daily dosing frequency.

688 Based on the dose-ranging trials in asthma and COPD, once-daily doses of fluticasone
689 furoate/vilanterol 50 mcg/25 mcg, 100 mcg/25 mcg, and 200 mcg/25 mcg were evaluated in the
690 confirmatory COPD trials.

691 **14.2 Confirmatory Trials**

692 The clinical development program for BREO ELLIPTA included 4 confirmatory trials in
693 subjects with COPD designed to evaluate the efficacy of BREO ELLIPTA on lung function
694 (Trials 1 and 2) and exacerbations (Trials 3 and 4).

695 **Lung Function:** Trials 1 and 2 were 24-week, randomized, double-blind, placebo-
696 controlled trials designed to evaluate the efficacy of BREO ELLIPTA on lung function in
697 subjects with COPD. In Trial 1, subjects were randomized to BREO ELLIPTA 100 mcg/25 mcg,
698 fluticasone furoate/vilanterol 200 mcg/25 mcg, fluticasone furoate 100 mcg, fluticasone furoate
699 200 mcg, vilanterol 25 mcg, and placebo. In Trial 2, subjects were randomized to BREO
700 ELLIPTA 100 mcg/25 mcg, fluticasone furoate/vilanterol 50 mcg/25 mcg, fluticasone furoate
701 100 mcg, vilanterol 25 mcg, and placebo. All treatments were administered as 1 inhalation once
702 daily.

703 Of the 2,254 patients, 70% were male and 84% were Caucasian. They had a mean age of
704 62 years and an average smoking history of 44 pack years, with 54% identified as current
705 smokers. At screening, the mean postbronchodilator percent predicted FEV₁ was 48% (range:
706 14% to 87%), mean postbronchodilator FEV₁/FVC ratio was 47% (range: 17% to 88%), and the
707 mean percent reversibility was 14% (range: -41% to 152%).

708 The co-primary efficacy variables in both trials were weighted mean FEV₁ (0 to 4 hours)
709 postdose on Day 168 and change from baseline in trough FEV₁ on Day 169 (the mean of the
710 FEV₁ values obtained 23 and 24 hours after the final dose on Day 168). The weighted mean
711 comparison of the fluticasone furoate/vilanterol combination with fluticasone furoate was

712 assessed to evaluate the contribution of vilanterol to BREO ELLIPTA. The trough FEV₁
713 comparison of the fluticasone furoate/vilanterol combination with vilanterol was assessed to
714 evaluate the contribution of fluticasone furoate to BREO ELLIPTA.

715 BREO ELLIPTA 100 mcg/25 mcg demonstrated a larger increase in the weighted mean
716 FEV₁ (0 to 4 hours) relative to placebo and fluticasone furoate 100 mcg at Day 168 (Table 2).
717

718 **Table 2. Least Squares Mean Change From Baseline in Weighted Mean FEV₁ (0-4 h)**
719 **and Trough FEV₁ 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 mcg/25 mcg	204	214 (161, 266)	168 (116, 220)	—	144 (91, 197)	45 (-8, 97)
Fluticasone furoate/vilanterol 200 mcg/25 mcg	205	209 (157, 261)	—	168 (117, 219)	131 (80, 183)	32 (-19, 83)
Trial 2						
BREO ELLIPTA 100 mcg/25 mcg	206	173 (123, 224)	120 (70, 170)	—	115 (60, 169)	48 (-6, 102)

720 ^a At Day 168.

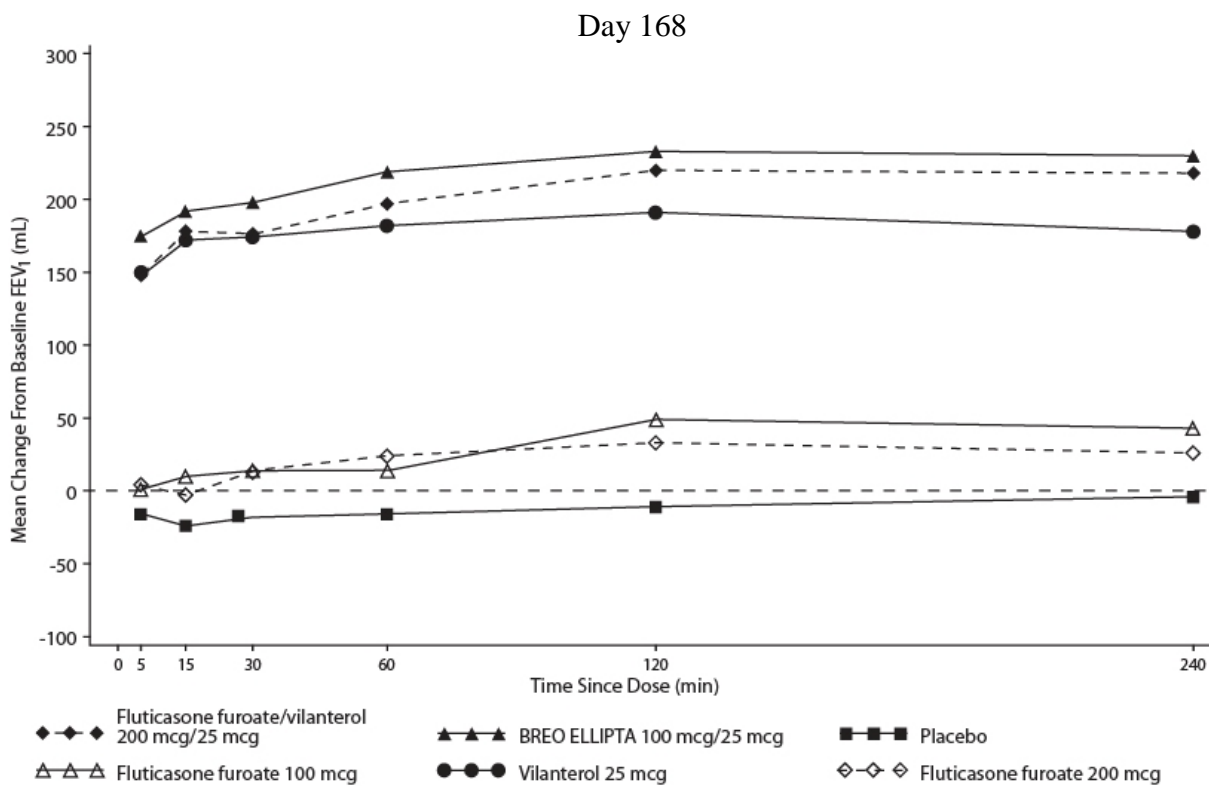
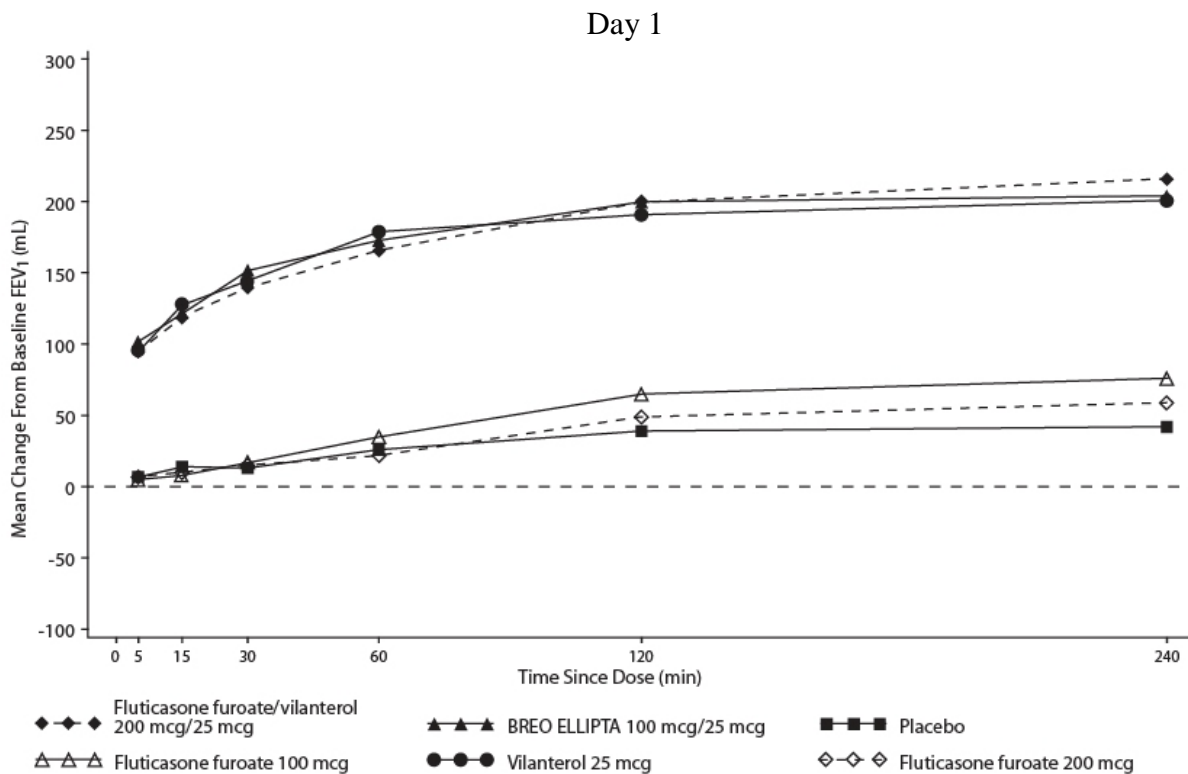
721 ^b At Day 169.

722

723 Serial spirometric evaluations were performed pre-dose and up to 4 hours after dosing.
724 Results from Trial 1 at Day 1 and Day 168 are shown in Figure 4. Similar results were seen in
725 Trial 2 (not shown).
726

727 **Figure 4. Raw Mean Change From Baseline in Post-Dose Serial FEV₁ (0-4 h, mL) on Days**
 728 **1 and 168**

729



734

735 The second co-primary variable was change from baseline in trough FEV₁ following the
736 final treatment day. At Day 169, both Trials 1 and 2 demonstrated significant increases in trough
737 FEV₁ for all strengths of the fluticasone furoate/vilanterol combination compared with placebo
738 (Table 2). The comparison of BREO ELLIPTA 100 mcg/25 mcg with vilanterol did not achieve
739 statistical significance (Table 2).

740 Trials 1 and 2 evaluated FEV₁ as a secondary endpoint. Peak FEV₁ was defined as the
741 maximum postdose FEV₁ recorded within 4 hours after the first dose of trial medicine on Day 1
742 (measurements recorded at 5, 15, and 30 minutes and 1, 2, and 4 hours). In both trials,
743 differences in mean change from baseline in peak FEV₁ were observed for the groups receiving
744 fluticasone furoate/vilanterol 100 mcg/25 mcg compared with placebo (152 and 139 mL,
745 respectively). The median time to onset, defined as a 100-mL increase from baseline in FEV₁,
746 was 16 minutes in subjects receiving fluticasone furoate/vilanterol 100 mcg/25 mcg.

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

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

763 Trials 3 and 4 included 3,255 subjects, of which 57% were male and 85% were
764 Caucasian. They had a mean age of 64 years and an average smoking history of 46 pack years,
765 with 44% identified as current smokers. At screening, the mean postbronchodilator percent
766 predicted FEV₁ was 45% (range: 12% to 91%), and mean postbronchodilator FEV₁/FVC ratio
767 was 46% (range: 17% to 81%), indicating that the subject population had moderate to very
768 severely impaired airflow obstruction. The mean percent reversibility was 15% (range: -65% to
769 313%).

770 Patients treated with BREO ELLIPTA 100 mcg/25 mcg had a lower annual rate of
771 moderate/severe COPD exacerbations compared with vilanterol in both trials (Table 3).

772

773 **Table 3. Moderate and Severe Chronic Obstructive Pulmonary Disease Exacerbations**

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

774

775 **16 HOW SUPPLIED/STORAGE AND HANDLING**

776 BREO ELLIPTA is supplied as a disposable light grey and pale blue plastic inhaler
777 containing 2 double-foil strips, each with 30 blisters. The inhaler is packaged within a moisture-
778 protective foil tray with a desiccant and a peelable lid (NDC 0173-0859-10).

779 BREO ELLIPTA is also supplied in an institutional pack as a disposable light grey and
780 pale blue plastic inhaler containing 2 double-foil strips, each with 14 blisters. It is packaged
781 within a moisture-protective foil tray with a desiccant and a peelable lid (NDC 0173-0859-14).

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

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

789 **17 PATIENT COUNSELING INFORMATION**

790 Advise the patient to read the FDA-approved patient labeling (Medication Guide and
791 Instructions for Use).

792 **17.1 Asthma-Related Death**

793 Patients should be informed that LABA, such as vilanterol, one of the active ingredients
794 in BREO ELLIPTA, increase the risk of asthma-related death. BREO ELLIPTA is not indicated
795 for the treatment of asthma.

796 **17.2 Not for Acute Symptoms**

797 BREO ELLIPTA is not meant to relieve acute symptoms of COPD and extra doses
798 should not be used for that purpose. Acute symptoms should be treated with a rescue inhaler
799 such as albuterol. The physician should provide the patient with such medicine and instruct the
800 patient in how it should be used.

801 Patients should be instructed to notify their physicians immediately if they experience
802 any of the following:

- 803 • Symptoms get worse
- 804 • Need for more inhalations than usual of their rescue inhaler
- 805 • Significant decrease in lung function as outlined by the physician

806 Patients should not stop therapy with BREO ELLIPTA without physician/provider
807 guidance since symptoms may recur after discontinuation.

808 **17.3 Do Not Use Additional Long-Acting Beta₂-Agonists**

809 When patients are prescribed BREO ELLIPTA, other medicines containing a LABA
810 should not be used.

811 **17.4 Risks Associated With Corticosteroid Therapy**

812 Local Effects: Patients should be advised that localized infections with *Candida albicans*
813 occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it
814 should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still
815 continuing therapy with BREO ELLIPTA, but at times therapy with BREO ELLIPTA may need
816 to be temporarily interrupted under close medical supervision. Rinsing the mouth without
817 swallowing after inhalation is advised to help reduce the risk of thrush.

818 Pneumonia: Patients with COPD who have received BREO ELLIPTA have a higher
819 risk of pneumonia and should be instructed to contact their healthcare providers if they develop
820 symptoms of pneumonia (e.g., fever, chills, change in sputum color, increase in breathing
821 problems).

822 Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids
823 should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their
824 physicians without delay. Patients should be informed of potential worsening of existing
825 tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex.

826 Hypercorticism and Adrenal Suppression: Patients should be advised that BREO
827 ELLIPTA may cause systemic corticosteroid effects of hypercorticism and adrenal suppression.
828 Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred
829 during and after transfer from systemic corticosteroids.

830 Reduction in Bone Mineral Density: Patients who are at an increased risk for
831 decreased BMD should be advised that the use of corticosteroids may pose an additional risk.

832 **Ocular Effects:** Long-term use of inhaled corticosteroids may increase the risk of some
833 eye problems (cataracts or glaucoma); regular eye examinations should be considered.

834 **17.5 Risks Associated With Beta-Agonist Therapy**

835 Patients should be informed of adverse effects associated with beta₂-agonists, such as
836 palpitations, chest pain, rapid heart rate, tremor, or nervousness.

837 **17.6 Hypersensitivity Reactions, Including Anaphylaxis**

838 Advise patients that hypersensitivity reactions (e.g., anaphylaxis, angioedema, rash,
839 urticaria) may occur after administration of BREO ELLIPTA. Instruct patients to discontinue
840 BREO ELLIPTA if such reactions occur. There have been reports of anaphylactic reactions in
841 patients with severe milk protein allergy after inhalation of other powder medications containing
842 lactose; therefore, patients with severe milk protein allergy should not use BREO ELLIPTA.

843

844 BREO and ELLIPTA are registered trademarks of the GSK group of companies.



845 BREO ELLIPTA was developed in collaboration with Theravance .

846

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848

849 GlaxoSmithKline

850 Research Triangle Park, NC 27709

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854 BRE:3PI

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MEDICATION GUIDE

857

BREO[®] ELLIPTA[®] (BREE-oh ee-LIP-ta)

858

(fluticasone furoate and vilanterol inhalation powder)

859

860 Read the Medication Guide that comes with BREO ELLIPTA before you start using it
861 and each time you get a refill. There may be new information. This Medication
862 Guide does not take the place of talking to your healthcare provider about your
863 medical condition or treatment.

864

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

867 **BREO ELLIPTA is only approved for use in chronic obstructive pulmonary**
868 **disease (COPD). BREO ELLIPTA is NOT approved for use in asthma.**

869 **BREO ELLIPTA can cause serious side effects, including:**

- 870 • **People with asthma who take long-acting beta₂-adrenergic agonist**
871 **(LABA) medicines, such as vilanterol (one of the medicines in BREO**
872 **ELLIPTA), have an increased risk of death from asthma problems.** It is
873 not known whether fluticasone furoate, the other medicine in BREO ELLIPTA,
874 reduces the risk of death from asthma problems seen with LABA medicines.
- 875 • **It is not known if LABA medicines, such as vilanterol (one of the**
876 **medicines in BREO ELLIPTA), increase the risk of death in people with**
877 **COPD.**
- 878 • **Call your healthcare provider if breathing problems worsen over time**
879 **while using BREO ELLIPTA.** You may need different treatment.
- 880 • **Get emergency medical care if:**
 - 881 • your breathing problems worsen quickly
 - 882 • you use your rescue inhaler, but it does not relieve your breathing problems.

883

884 **What is BREO ELLIPTA?**

885 BREO ELLIPTA combines an inhaled corticosteroid (ICS) medicine, fluticasone
886 furoate, and a LABA medicine, vilanterol.

- 887 • ICS medicines, such as fluticasone furoate (one of the medicines in BREO
888 ELLIPTA), help to decrease inflammation in the lungs. Inflammation in the lungs
889 can lead to breathing problems.
- 890 • LABA medicines, such as vilanterol (one of the medicines in BREO ELLIPTA), help
891 the muscles around the airways in your lungs stay relaxed to prevent symptoms
892 such as wheezing, cough, chest tightness, and shortness of breath. These
893 symptoms can happen when the muscles around the airways tighten. This
894 makes it hard to breathe.

895 BREO ELLIPTA is used for COPD. COPD is a chronic lung disease that includes
896 chronic bronchitis, emphysema, or both. BREO ELLIPTA is a prescription medicine
897 that is used long term as 1 inhalation 1 time each day to improve symptoms of
898 COPD for better breathing and to reduce the number of flare-ups (the worsening of
899 your COPD symptoms for several days).

- 900 • **BREO ELLIPTA is not for use to treat sudden symptoms of COPD.** Always
901 have a rescue inhaler (an inhaled, short-acting bronchodilator) with you to treat
902 sudden symptoms. If you do not have a rescue inhaler, contact your healthcare
903 provider to have one prescribed for you.
- 904 • **BREO ELLIPTA is not for the treatment of asthma. It is not known if**
905 **BREO ELLIPTA is safe and effective in people with asthma.**

- 906 • BREO ELLIPTA should not be used in children. It is not known if BREO ELLIPTA is
907 safe and effective in children.

908

909 **Who should not use BREO ELLIPTA?**

910 Do not use BREO ELLIPTA if you:

- 911 • have a severe allergy to milk proteins. Ask your healthcare provider if you are
912 not sure.
913 • are allergic to fluticasone furoate, vilanterol, or any of the ingredients in BREO
914 ELLIPTA. See “What are the ingredients in BREO ELLIPTA?” below for a complete
915 list of ingredients.

916

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

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

- 920 • have heart problems
921 • have high blood pressure
922 • have seizures
923 • have thyroid problems
924 • have diabetes
925 • have liver problems
926 • have weak bones (osteoporosis)
927 • have an immune system problem
928 • have eye problems such as glaucoma or cataracts
929 • are allergic to any of the ingredients in BREO ELLIPTA, any other medicines, or
930 food products. See “What are the ingredients in BREO ELLIPTA?” below for a
931 complete list of ingredients.
932 • have any type of viral, bacterial, or fungal infection
933 • are exposed to chickenpox or measles or been around anyone who has
934 chickenpox or measles
935 • have any other medical conditions
936 • are pregnant or planning to become pregnant. It is not known if BREO ELLIPTA
937 may harm your unborn baby.
938 • are breastfeeding. It is not known if the medicines in BREO ELLIPTA pass into
939 your milk and if they can harm your baby.

940 **Tell your healthcare provider about all the medicines you take**, including
941 prescription and non-prescription medicines, vitamins, and herbal supplements.
942 BREO ELLIPTA and certain other medicines may interact with each other. This may
943 cause serious side effects. Especially, tell your healthcare provider if you take
944 antifungal or anti-HIV medicines.

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

947

948 **How should I use BREO ELLIPTA?**

949 **Read the step-by-step instructions for using BREO ELLIPTA at the end of**
950 **this Medication Guide.**

- 951 • **Do not** use BREO ELLIPTA unless your healthcare provider has taught you how
952 to use the inhaler and you understand how to use it correctly.
- 953 • Use BREO ELLIPTA exactly as prescribed. **Do not** use BREO ELLIPTA more often
954 than prescribed.
- 955 • Use 1 inhalation of BREO ELLIPTA 1 time each day. Use BREO ELLIPTA at the
956 same time each day.
- 957 • If you miss a dose of BREO ELLIPTA, take it as soon as you remember. Do not
958 take more than 1 inhalation per day. Take your next dose at your usual time. Do
959 not take 2 doses at one time.
- 960 • If you take too much BREO ELLIPTA, call your healthcare provider and get
961 medical help right away if you have any unusual symptoms, such as worsening
962 shortness of breath, chest pain, increased heart rate, or shakiness.
- 963 • **Do not use other medicines that contain a LABA for any reason.** Ask your
964 healthcare provider or pharmacist if any of your other medicines are LABA
965 medicines.
- 966 • Do not stop using BREO ELLIPTA unless told to do so by your healthcare
967 provider because your symptoms might get worse. Your healthcare provider will
968 change your medicines as needed.
- 969 • **BREO ELLIPTA does not relieve sudden symptoms.** Always have a rescue
970 inhaler with you to treat sudden symptoms. If you do not have a rescue inhaler,
971 call your healthcare provider to have one prescribed for you.
- 972 • Call your healthcare provider or get medical care right away if:
973 • your breathing problems get worse
974 • you need to use your rescue inhaler more often than usual
975 • your rescue inhaler does not work as well to relieve your symptoms
976 • you need to use 4 or more inhalations of your rescue inhaler in 24 hours for
977 2 or more days in a row
978 • you use 1 whole canister of your rescue inhaler in 8 weeks

979

980 **What are the possible side effects with BREO ELLIPTA?**

- 981 **BREO ELLIPTA can cause serious side effects, including:**
- 982 • **See “What is the most important information I should know about BREO**
- 983 **ELLIPTA?”**
- 984 • **pneumonia.** People with COPD have a higher chance of getting pneumonia.
- 985 BREO ELLIPTA may increase the chance of getting pneumonia. Call your
- 986 healthcare provider if you notice any of the following symptoms:
- 987 • increase in mucus (sputum) production
- 988 • change in mucus color
- 989 • fever
- 990 • chills
- 991 • increased cough
- 992 • increased breathing problems
- 993 • **thrush (fungal infection) in mouth and throat.** You may develop a yeast
- 994 infection (*Candida albicans*) in your mouth or throat. Rinse your mouth with
- 995 water without swallowing after using BREO ELLIPTA to help prevent thrush in
- 996 your mouth and throat.
- 997 • **serious allergic reactions.** Call your healthcare provider or get emergency
- 998 medical care if you get any of the following symptoms of a serious allergic
- 999 reaction:
- 1000 • rash
- 1001 • hives
- 1002 • swelling of the face, mouth, and tongue
- 1003 • breathing problems
- 1004 • **sudden breathing problems immediately after inhaling your medicine**
- 1005 • **effects on heart**
- 1006 • increased blood pressure
- 1007 • a fast and/or irregular heartbeat
- 1008 • chest pain
- 1009 • **effects on nervous system**
- 1010 • tremor
- 1011 • nervousness
- 1012 • **reduced adrenal function (adrenal insufficiency).** Adrenal insufficiency is a
- 1013 condition in which the adrenal glands do not make enough steroid hormones.
- 1014 This can happen when you stop taking oral corticosteroid medicines (such as
- 1015 prednisone) and start taking a medicine containing an inhaled corticosteroid
- 1016 (such as BREO ELLIPTA). When your body is under stress from fever, trauma

1017 (such as a car accident), infection, surgery, or worse COPD symptoms, adrenal
1018 insufficiency can get worse and may cause death.

1019 Symptoms of adrenal insufficiency include:

- 1020 • feeling tired (fatigue)
- 1021 • lack of energy
- 1022 • weakness
- 1023 • nausea and vomiting
- 1024 • low blood pressure

1025 • **changes in laboratory blood values (sugar, potassium)**

1026 • **weakened immune system and increased chance of getting infections**
1027 **(immunosuppression)**

1028 • **bone thinning or weakness (osteoporosis)**

1029 • **eye problems including glaucoma and cataracts.** You should have regular
1030 eye exams while using BREO ELLIPTA.

1031 **Common side effects of BREO ELLIPTA include:**

- 1032 • runny nose and sore throat
- 1033 • upper respiratory tract infection
- 1034 • headache
- 1035 • thrush in the mouth and/or throat. Rinse your mouth without swallowing after
1036 use to help prevent this.

1037 Tell your healthcare provider about any side effect that bothers you or that does
1038 not go away.

1039 These are not all the side effects with BREO ELLIPTA. Ask your healthcare provider
1040 or pharmacist for more information.

1041 Call your doctor for medical advice about side effects. You may report side effects
1042 to FDA at 1-800-FDA-1088.

1043

1044 **How do I store BREO ELLIPTA?**

- 1045 • Store BREO ELLIPTA at room temperature between 68°F and 77°F (20°C and
1046 25°C). Keep in a dry place away from heat and sunlight.
- 1047 • Store BREO ELLIPTA in the unopened foil tray and only open when ready for
1048 use.
- 1049 • Safely throw away BREO ELLIPTA in the trash 6 weeks after you open the foil
1050 tray or when the counter reads "0", whichever comes first. Write the date you
1051 open the tray on the label on the inhaler.

- 1052 • **Keep BREO ELLIPTA and all medicines out of the reach of children.**
1053

1054 **General Information about BREO ELLIPTA**

1055 Medicines are sometimes prescribed for purposes not mentioned in a Medication
1056 Guide. Do not use BREO ELLIPTA for a condition for which it was not prescribed. Do
1057 not give your BREO ELLIPTA to other people, even if they have the same condition
1058 that you have. It may harm them.

1059 This Medication Guide summarizes the most important information about BREO
1060 ELLIPTA. If you would like more information, talk with your healthcare provider or
1061 pharmacist. You can ask your healthcare provider or pharmacist for information
1062 about BREO ELLIPTA that was written for healthcare professionals.

1063 For more information about BREO ELLIPTA, call 1-888-825-5249 or visit our
1064 website at www.myBREO.com.

1065

1066 **What are the ingredients in BREO ELLIPTA?**

1067 Active ingredients: fluticasone furoate, vilanterol

1068 Inactive ingredients: lactose monohydrate (contains milk proteins), magnesium
1069 stearate

1070

1071

Instructions for Use

1072 **For Oral Inhalation Only.**

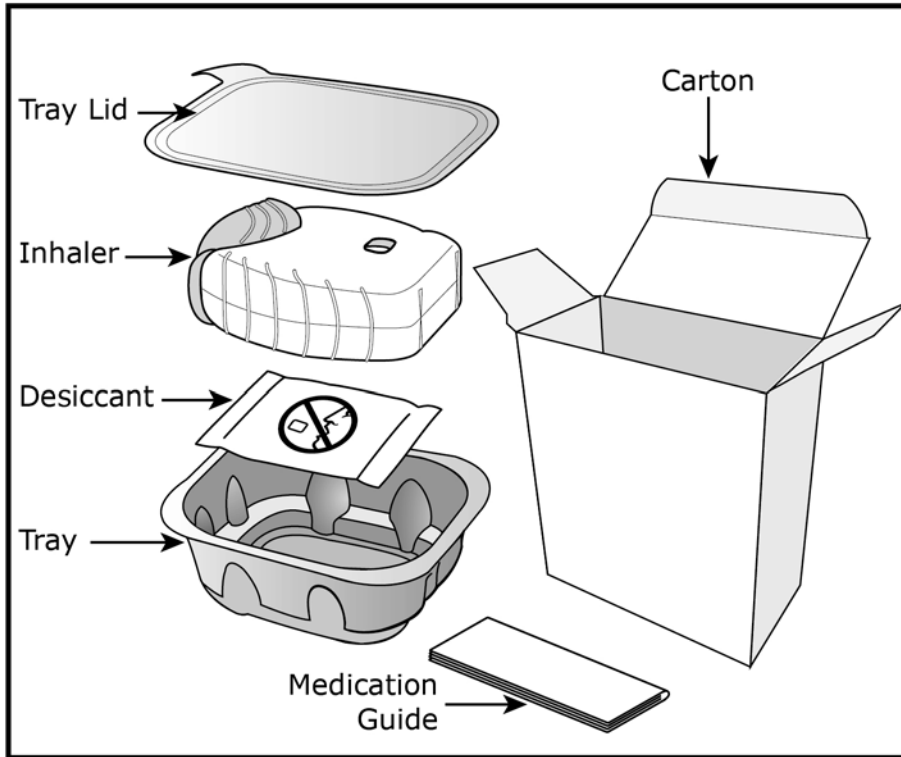
1073

1074 **Read this before you start:**

- 1075 • **If you open and close the cover without inhaling the medicine, you**
1076 **will lose the dose.**
- 1077 • **The lost dose will be securely held inside the inhaler, but it will no**
1078 **longer be available to be inhaled.**
- 1079 • **It is not possible to accidentally take a double dose or an extra dose**
1080 **in one inhalation.**

1081

1082 **Your BREO ELLIPTA inhaler**



1083

1084

1085 **How to use your inhaler**

- 1086 • BREO ELLIPTA comes in a foil tray.
- 1087 • Peel back the lid to open the tray. See Figure A.
- 1088 • The tray contains a desiccant to reduce moisture. Do not eat or inhale. Throw
- 1089 it away in the household trash out of reach of children and pets. See Figure B.

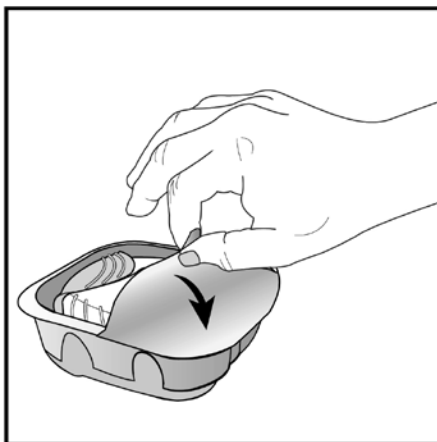


Figure A

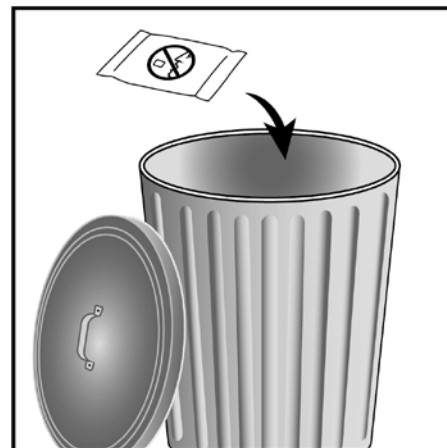


Figure B

Important Notes:

- Your inhaler contains 30 doses (14 doses if you have a sample or institutional pack).
- Each time you open the cover of the inhaler fully (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 one 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.

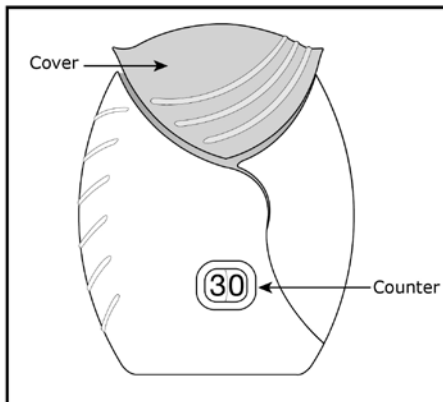


Figure C

- 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.

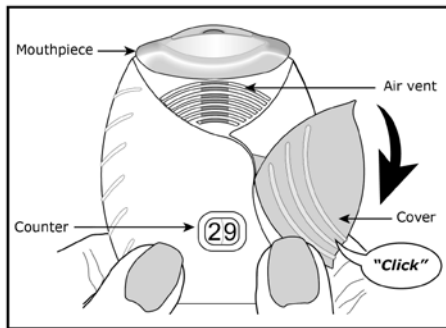


Figure D

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.

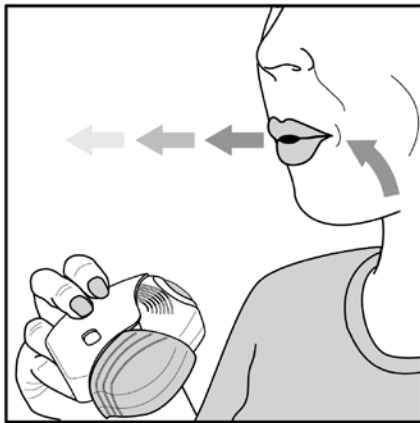


Figure E

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.

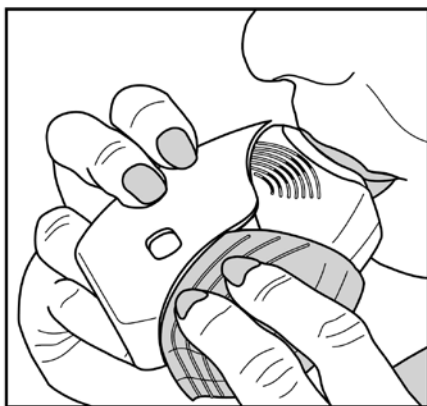


Figure F

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.

Do not block the air vent with your fingers.

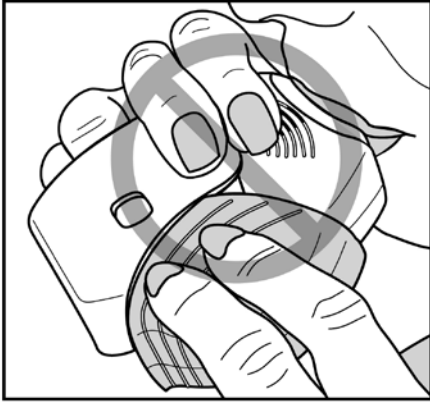


Figure G

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

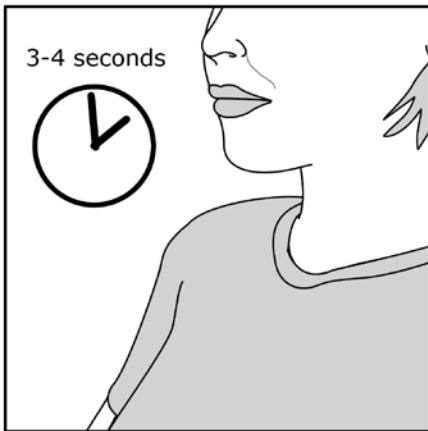


Figure H

- 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.

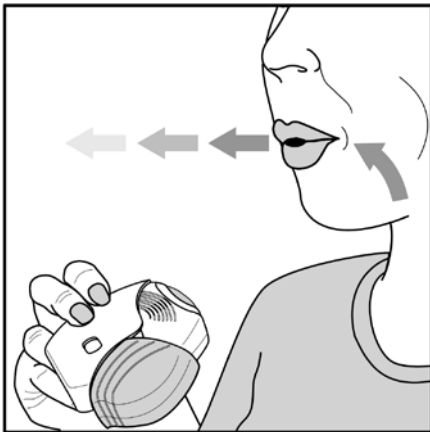


Figure I

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.

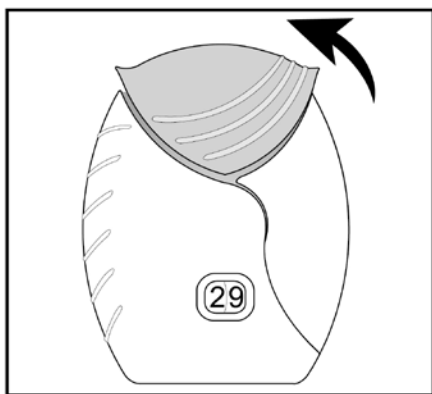


Figure J

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?

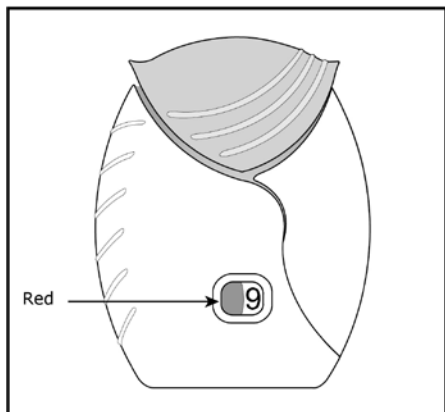



Figure L

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

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BREO ELLIPTA was developed in collaboration with Theravance  .



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