Drug Monograph

Drug/Drug Class:	**Breo™ Ellipta™ (Fluticasone Furoate/Vilanterol Trifenatate) Inhalation/ Corticosteroid and long acting beta-2-adrenergic agonist combination agent**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each inhaler contains 2 blister strips of powder, one strip contains fluticasone furoate 100 mcg per blister and the other contains vilanterol 25 mcg per blister. GlaxoSmithKline Research Triangle Park, NC 27709
Summary of Findings:	Breo™ Ellipta™ has demonstrated efficacy by reducing the number of COPD exacerbations in patients with COPD, including chronic bronchitis and/or emphysema, with a history of exacerbations when compared with vilanterol monotherapy. It is not indicated for the treatment of acute exacerbations.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

COPD is the fourth leading cause of death in the United States and it is estimated to affect 3 million people in the US. It is estimated that the prevalence of emphysema is 18 cases per 1000 people and chronic bronchitis is 34 cases per 1000 people.

Dosage Form(s)[1]

Each inhaler contains 2 blister strips of powder, one strip contains fluticasone furoate 100 mcg per blister and the other contains vilanterol trifenatate 25 mcg per blister. There are 30 blisters on each blister strip.

Manufacturer

GlaxoSmithKline Research Triangle Park, NC 27709

Indication(s)[1]

Breo Ellipta is indicated for long-term, once daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

Clinical Efficacy[1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Fluticasone furoate is a synthetic trifluorinated corticosteroid and vilanterol trifenatate is a long-acting beta-2-adrenergic agonist. Fluticasone furoate exerts anti-inflammatory effects but its exact mechanism of action in COPD is unknown. Vilanterol trifenatate increases cyclic adenosine monophosphate (cAMP) levels, resulting in relaxation of bronchial smooth muscle and inhibition of mast cell release of immediate hypersensitivity mediators.

	Fluticasone Furoate	Vilanterol Trifenatate
Protein binding	99.6%	93.9%
Volume of distribution	661 L	165 L
Metabolism	Hepatic, via CYP3A4	Hepatic, via CYP3A4
Excretion	Feces (90% to 101%) Urine (1% to 2%)	Feces (30%) Urine (70%)
Half-life	24 hours	21.3 hours

The effect of Breo Ellipta on lung function in the treatment of COPD was studied in 2 large, multicenter, randomized, double-blind, placebo-controlled clinical trials. In each trial, fluticasone

100 mcg/vilanterol 25 mcg improved the mean weighted FEV1 (0 to 4 hours) and the change from baseline in trough FEV1 at 6 months compared with placebo. In 2 separate randomized, double-blind clinical trials, fluticasone 100 mcg/vilanterol 25 mcg was associated with fewer moderate to severe COPD exacerbations when compared with vilanterol monotherapy.

COPD – STUDY 1

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 24-week, multicenter clinical trial (n=1030).
INCLUSION CRITERIA	Patients 40 years or older with a clinical diagnosis of stable, moderate-to-severe COPD and a 10-year or more pack history of smoking.
EXCLUSION CRITERIA	Any concomitant non-COPD respiratory disorder, lung volume reduction surgery within the previous year, acute worsening of COPD requiring corticosteroids or antibiotics or a lower respiratory tract infection requiring antibiotics within the previous 6 weeks, hospitalization for COPD within the previous 12 weeks, or long-term or nocturnal (at least 12 hours/day) oxygen therapy.
TREATMENT REGIMEN	Following a 2-week screening period to assess baseline lung function, patients were randomized to receive fluticasone 100 mcg/vilanterol 25 mcg (n=206), fluticasone 50 mcg/vilanterol 25 mcg (n=206), fluticasone furoate 100 mcg (n=206), vilanterol 25 mcg (n=205), or placebo (n=207) once daily for 24 weeks. The coprimary endpoints were weighted mean FEV1 (0 to 4 hours) postdose and the change from baseline in trough FEV1 at 6 months.
RESULTS	The mean baseline postbronchodilator FEV1 in each treatment group ranged from 1.32 to 1.448 L. Fluticasone 100 mcg/vilanterol 25 mcg was associated with mean weighted FEV1 (0 to 4 hours) increases of 173 mL (95% CI, 123 to 224 mL; $p < 0.001$) and 120 mL (95% CI, 70 to 170 mL; $p < 0.001$) compared with placebo and fluticasone furoate 100 mcg, respectively. Fluticasone 100 mcg/vilanterol 25 mcg demonstrated a significantly greater trough FEV1 value compared with placebo (mean difference, 115 mL; 95% CI, 60 to 169 mL; $p < 0.001$), but not compared with fluticasone furoate 100 mcg (mean difference, 82 mL; 95% CI, 28 to 136 mL) or vilanterol 25 mcg (mean difference, 48 mL; 95% CI, 6 to 102 mL; p=0.082). The group treated with fluticasone 50 mcg/vilanterol 25 mcg demonstrated mean weighted FEV1 (0 to 4 hours) increases of 192 mL (95% CI, 141 to 243 mL) and 90 mL (95% CI, 39 to 140 mL) compared with placebo and vilanterol 25 mcg, respectively, although no statistical inferences could be made due to the statistical hierarchy used in the analysis.
SAFETY	Local steroid effects (ie, oropharyngeal candidiasis, oral candidiasis) and upper respiratory tract infections were reported more frequently among patients allocated to either fluticasone/vilanterol group compared with the other 3 treatment arms.

COPD – STUDY 2

STUDY DESIGN	Randomized, double-blind, placebo-controlled, 24-week, multicenter clinical trial (n=1224).
INCLUSION CRITERIA	Patients 40 years or older with a clinical diagnosis of stable, moderate-to-severe COPD and a 10-year or more pack history of smoking.
EXCLUSION CRITERIA	Any concomitant non-COPD respiratory disorder, lung volume reduction surgery within the previous year, acute worsening of COPD requiring corticosteroids or antibiotics or a lower respiratory tract infection requiring antibiotics within the previous 6 weeks, hospitalization for COPD within the previous 12 weeks, or long-term or nocturnal (at least 12 hours/day) oxygen therapy.
TREATMENT REGIMEN	Following a 2-week screening period to assess baseline lung function, patients were randomized to receive fluticasone 100 mcg/vilanterol 25 mcg (n=204), fluticasone 200 mcg/vilanterol 25 mcg (n=205), fluticasone furoate 100 mcg (n=204), fluticasone furoate 200 mcg (n=203), vilanterol 25 mcg (n=203), or placebo (n=205) once daily for 24 weeks. The co-primary endpoints were weighted mean FEV1 (0 to 4 hours) postdose and the change from baseline in trough FEV1 at 6 months.
RESULTS	At baseline, the mean post-bronchodilator FEV1 of each treatment group ranged from 1.436 L to 1.532 L. Fluticasone 200 mcg/vilanterol 25 mcg was associated with increases in mean weighted FEV1 (0 to 4 hours) of 209 mL (95% CI, 157 to 261 mL) and 168 mL (95% CI, 117 to 219 mL) compared with placebo and fluticasone furoate 200 mcg, respectively ($p < 0.001$ for both comparisons). Fluticasone 100 mcg/vilanterol 25 mcg was associated with mean weighted FEV1 (0 to 4 hours) increases of 214 mL (95% CI, 161 to 266 mL) and 168 mL (95% CI, 116 to 220 mL) compared with placebo and fluticasone furoate 100 mcg, respectively; no statistical inferences could be made for comparisons with fluticasone 100 mcg/vilanterol 25 mcg due to the statistical hierarchy used in the analysis. Both doses of fluticasone/vilanterol resulted in higher trough FEV1 values compared with placebo, with observed differences of 131 mL (95% CI, 80 to 183 mL; $p < 0.001$) in the fluticasone 200 mcg/vilanterol 25 mcg group and 144 mL (95% CI, 91 to 197 mL; no statistical analysis performed) in the fluticasone 100 mcg/vilanterol 25 mcg group.
SAFETY	The incidence and types of adverse effects were similar among all treatment groups, and were not observed more frequently compared with the placebo group.

COPD - EXACERBATIONS

STUDY DESIGN	Two randomized, double-blind, 52-week clinical trials (n=3255).
INCLUSION CRITERIA	Not specified
EXCLUSION CRITERIA	Not specified
TREATMENT REGIMEN	After a 4-week run-in period, during which fluticasone propionate 250 mcg/salmeterol 50 mcg twice daily was administered, patients (mean age, 64 years; 57% male; 85% Caucasian; average smoking history, 46 pack-years) were randomized to receive fluticasone 100 mcg/vilanterol 25 mcg, fluticasone 50 mcg/vilanterol 25 mcg, fluticasone 200 mcg/vilanterol 25 mcg, or vilanterol 25 mcg. The primary endpoint was the annual rate of moderate or severe exacerbations. Exacerbations were defined as the worsening of 2 or more major symptoms (dyspnea, sputum volume, sputum purulence), or worsening of 1 major symptom plus 1 minor symptom (sore throat, cold, fever without other cause, increased cough or wheeze for 2 consecutive days). Exacerbations were moderate if systemic steroids and/or antibiotics were necessary, and exacerbations were severe if hospitalization was required.
RESULTS	In trial 1, patients who received fluticasone 100 mcg/vilanterol 25 mcg (n=403) experienced a mean of 0.9 moderate or severe exacerbations/year compared with a mean of 1.14 moderate or severe exacerbations/year for patients who received vilanterol 25 mcg (n=409; ratio versus vilanterol, 0.79; 95% CI, 0.64 to 0.97). In trial 2, patients who received fluticasone 100 mcg/vilanterol 25 mcg (n=403) experienced a mean of 0.7 moderate or severe exacerbations/year compared with a mean of 1.05 moderate or severe exacerbations/year for patients who received vilanterol 25 mcg (n=409; ratio versus vilanterol, 0.66; 95% CI, 0.54 to 0.81).
SAFETY	Not specified

Contraindications[1]

- Hypersensitivity to milk proteins, severe
- Hypersensitivity to fluticasone furoate, vilanterol, or any excipient

Warnings and Precautions[1]

- Asthma-related death and serious asthma events; increased risk due to long-acting beta 2-agonist (vilanterol) component; use not indicated for asthma.
- Asthma treatment; use not indicated.
- Bronchospasm, acute; use not indicated.
- COPD, rapidly deteriorating or potentially life-threatening; do not initiate treatment with fluticasone/vilanterol.
- Adrenal response, inadequate; especially in postoperative patients or during times of stress; due to systemic absorption of corticosteroid.
- Bone mineral density loss has been reported with long-term inhaled corticosteroid use; increased risk with prolonged immobilization, family history of osteoporosis, postmenopausal

status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that reduce bone mass (eg, anticonvulsants, oral corticosteroids); monitoring recommended.
- Bronchospasm, paradoxical and potentially fatal, may occur; discontinue immediately and initiate alternative therapy.
- Cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; potential exacerbation due to vilanterol component.
- Concomitant use with other long-acting beta 2-agonists not recommended.
- Concomitant use with strong CYP3A4 inhibitors (eg, ketoconazole, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, and voriconazole); caution advised.
- Convulsive disorders; potential exacerbation due to vilanterol component.
- Corticosteroid, systemic use, switching from systemic therapy to inhaled corticosteroid; deaths due to adrenal insufficiency have been reported.
- Corticosteroid effects, systemic (eg hypercorticism, adrenal suppression); increased risk with higher than recommended doses, coadministration of a strong CYP3A4 inhibitor, or recommended doses in susceptible patients.
- Diabetes mellitus and ketoacidosis; potential exacerbation due to vilanterol component.
- Exceeding the recommended dose; increased risk of fatality or significant cardiovascular events, due to beta 2-agonist (vilanterol) component.
- Glaucoma, cataracts, and increased intraocular pressure have been reported with long-term inhaled corticosteroid use; monitoring recommended, particularly in patients with a history of these conditions and a change in vision.
- Hypokalemia, significant, due to vilanterol component, has been reported; increased risk of cardiovascular effects.
- Immunosuppression; increased risk of infections, such as chicken pox and measles; prophylaxis with immune globulin may be indicated.
- Infection, localized, of mouth or pharynx due to Candida albicans, has been reported; may require systemic antifungal treatment and interruption of inhalation therapy.
- Infection, systemic fungal, bacterial, viral, parasitic, or ocular herpes simplex; use with caution due to fluticasone component.
- Pneumonia, occasionally fatal or requiring hospitalization, has been reported.
- Thyrotoxicosis; potential exacerbation due to vilanterol component.
- TB, active or quiescent; use with caution due to fluticasone component.

Adverse Effects[1]

Most common ≥ 3%	BREO ELLIPTA (n=410)	PLACEBO (n=412)
Naspharyngitis	9%	8%
Headache	7%	5%
Upper respiratory tract infection	7%	3%
Oropharyngeal candidiasis	5%	2%

Drug Interactions[1]

- Beta blockers
- CYP3A4 inhibitors, strong: clarithromycin, ketoconazole
- Diuretics, non-potassium-sparing (loop or thiazide diuretics)
- Drugs known to prolong the QTc interval
- Monoamine oxidase inhibitors

- Tricyclic antidepressants

Dosage and Administration[1]

The recommended dose is one oral inhalation (Breo Ellipta 100 mcg/ 25 mcg) once daily at the same time each day, followed by a mouth rinse without swallowing to reduce the risk of oropharyngeal candidiasis.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*
Fluticasone Furoate/Vilanterol Trifenatate	**Breo Ellipta**	**GlaxoSmithKline**	**100-25mcg**	**1 inhalation daily**	**$ 4.46 per inhalation**

***W**holesale **A**cquisition **C**ost

Conclusion

The combination of fluticasone furoate and vilanterol trifenatate has demonstrated efficacy in improving lung function as long-term maintenance treatment of COPD when compared to placebo and in reducing the number of COPD exacerbations when compared to vilanterol alone. It is the first combination inhaled corticosteroid/long-acting beta-2-adrenergic agonist that is administered once daily. Breo Ellipta was well-tolerated in large clinical trials.

Recommendation

The Division recommends this product be considered for inclusion to the state specific PDL edit and it is currently under solicitation.

References

1. Product Information: Breo™ Ellipta™, fluticasone furoate/vilanterol oral inhalation powder. GlaxoSmithKline, Research Triangle Park, NC, 05/2013.

2. Kerwin EM, Scott-Wilson C, Sanford L et al: A randomised trial of fluticasone furoate/vilanterol (50/25 mcg; 100/25 mcg) on lung function in COPD. Respir Med 2013; 107(4):560-569.

3. Martinez FJ, Boscia J, Feldman G et al: Fluticasone furoate/vilanterol (100/25; 200/25 mcg) improves lung function in COPD: a randomised trial. Respir Med 2013; 107(4):550-559.

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