PDL NEW DRUG REVIEW

Proprietary Name: Breo Ellipta®
Common Name: fluticasone furoate/vilanterol
PDL Category: Inhaled Glucocorticoid Combo

Comparable Products	Preferred Drug List Status
Advair	Preferred
Dulera	Preferred
Symbicort	Preferred

Summary

Indications and Usage: For the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. Breo Ellipta® is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma. A box warning associated with Breo Ellipta® indicates that the safety and efficacy for use in those with asthma has not been established. This is a pregnancy category C medication. The safety and efficacy of use in children under 18 years of age has not been established.

Drug Interactions: Both active ingredients are CYP3A4 substrates. Therefore, caution should be used if given concomitantly with ketoconazole and other known strong CYP3A4 inhibitors. Vilanterol should be used with extreme caution in those currently being treated with MAO Inhibitors, TCAs, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents. The use of beta-adrenergic receptor blocking agents should be avoided in those with COPD; they also block the effects of vilanterol. In addition, use caution when giving the combination of beta-agonists with non-potassium-sparing diuretics.

Dosage Forms: Inhalation powder, 30 blisters containing powder for oral inhalation; 100mcg/blister of fluticasone and 25mcg/blister of vilanterol

Recommended Dosage: One inhalation once daily by the orally inhaled route only; the mouth should be rinsed with water without swallowing to help reduce the risk of oropharyngeal candidiasis. Take at the same time every day, with no more than 1 inhalation every 24 hours. Dosage adjustments are not required in those with hepatic or renal impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse event reported with Breo Ellipta® includes nasopharyngitis (1%), upper respiratory tract infection (4%), oropharyngeal candidiasis (3%), and headache (2%).

Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for fluticasone. The most common adverse event reported with Breo Ellipta® includes nasopharyngitis (1%), upper respiratory tract infection (3%), oropharyngeal candidiasis (2%), and headache (0%).

Due to the vilanterol component, Breo Ellipta® has a boxed warning regarding the risk of asthma-related death, as long-acting beta2-adrenergic agonists (LABAs) increase the risk of asthma-related death. Although the finding was with salmeterol, another LABA, the warning is considered a class effect.

Pneumonia has been reported in those with COPD receiving Breo Ellipta®. In a 12 month trial (N=3255), there was a higher incidence of pneumonia in those taking Breo Ellipta® (6-7%) as compared with those taking vilanterol (3%). Inhaled corticosteroids should be used with caution in those with active or quiescent TB infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. In addition, while hypercorticism and adrenal

suppression are known effects of corticosteroids, the effects of fluticasone on the HPA axis are not seen with therapeutic doses of Breo Ellipta®. Nevertheless, exceeding the recommended dose or using in combination with a strong CYP3A4 inhibitor may cause HPA axis dysfunction.

Contraindications: In those with known hypersensitivity to milk proteins or hypersensitivity to fluticasone, vilanterol, or any component of the compound.

Manufacturer: GlaxoSmithKline

Analysis: Breo Ellipta® is a combination of fluticasone furoate (a synthetic corticosteroid) and vilanterol (a LABA). Fluticasone has anti-inflammatory activity, by working on a range of multiple cell types (eg mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (eg histamine, eicosanoids, leukotrienes, cytokines). Beta2-receptors are the primary receptors in bronchial smooth muscle, and they cause relaxation of bronchial smooth muscle.

To validate the safety and efficacy of Breo Ellipta®, there were 4 confirmatory studies of 6-12 months duration, dose-ranging studies, and 3 active comparator trials that were of 12 weeks duration. Two of the registration studies (trial 3 and trial 4; N=3,255) assessed the mean annual rate of COPD exacerbations per year. Those in the Breo Ellipta® group had a lower annual rate of moderate/severe COPD exacerbations as compared with vilanterol in trial 3 (0.90 vs 1.14) and trial 4 (0.70 vs 1.05). Two of the registration trials assessed lung function (Trial 1 and Trial 2; N=2,254), and results suggested that Breo Ellipta® demonstrated larger increases in weighted mean (wm) FEV as compared to placebo and fluticasone at day 168.

In a study by Martinez et al[2], fluticasone/vilanterol (f/v) was compared with placebo and its individual active ingredients in a double-blind, randomized study (N=1224). Statistically significant increases in weighted mean (wm) FEV1 (209ml) and trough FEV1 (131ml) was seen between f/v 200/25mcg vs placebo; however, similar changes were seen for f/v 100/25mcg vs placebo. Significant differences between f/v 200/25mcg and vilanterol were not seen in change from baseline trough FEV1 (32ml; p=0.224), but the difference between f/v 200/25mcg and fluticasone 200 was significant for wm FEV (168ml, p<0.001).

In a randomized, double-blind study by Kerwin et al[3] in those (N=1030) with moderate-to-severe COPD, fluticasone/vilanterol (f/v) was compared with placebo and individual ingredients to assess weighted mean (wm) FEV1 and trough FEV1. Results suggested that f/v 100/25mcg significantly improved wm FEV1 (173ml, p<0.001) and trough FEV1 (115ml; p<0.001) as compared with placebo. Significant differences between f/v 100/25mcg and vilanterol were not seen for trough FEV1 (48ml; p=0.082); however, a significant effect was seen between f/v 100/25mcg and fluticasone for wm FEV1 (120ml; p<0.001).

There is no evidence at this time to support that that Breo Ellipta® is more efficacious or safer than the currently available, more cost effective individual components (inhaled corticosteroids and LABAs) or other combination products. Therefore, it is recommended that Breo Ellipta® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Breo Ellipta [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013.

[2] Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25, 200/25mcg) improves lung function in COPD: a randomized trial. *Respir Med*. 2013; 107(4): 550-9.

[3] Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomized trial of fluticasone furoate/vilanterol (50/25mcg; 100/25mcg) on lung function in COPD. *Respir Med*. 2013; 107(4): 560-9.