

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204275Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation (REMS) Review

Date: April 22, 2013

Reviewer(s): Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK)  
Kendra Worthy, Pharm. D., Team Leader, DRISK

Division Director: Claudia Manzo, Pharm. D., DRISK

Drug Name(s): Breo Ellipta (fluticasone furoate/vilanterol) oral inhalation powder

Therapeutic Class: Inhaled corticosteroid (ICS)/long-acting beta<sub>2</sub>-agonist (LABA)

Indication(s): For 1) Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) and 2) Reduction of COPD exacerbations.

Dose(s): One oral inhalation of fluticasone furoate 100 mcg/vilanterol 25 mcg once daily

Subject: Review to evaluate the need for a Risk Evaluation and Mitigation Strategy (REMS)

Application Type/Number: NDA 204275

Applicant/sponsor: GlaxoSmithKline (GSK)

OSE RCM #: 2012-1686

## **1 INTRODUCTION**

This review by the Division of Risk Management (DRISK) evaluates whether a Risk Evaluation and Mitigation Strategy (REMS) for Breo Ellipta (fluticasone furoate / vilanterol) oral inhalation powder NDA 204275 is required.

## **2 BACKGROUND**

Breo Ellipta, a new molecular entity, is a combination of vilanterol trifenate (25 mcg), a long-acting beta<sub>2</sub>-adrenergic agonist (LABA) and fluticasone furoate (100 mcg), an inhaled corticosteroid (ICS). The proposed indication is maintenance treatment of chronic obstructive pulmonary disease (COPD) and reduction in COPD exacerbation. The proposed dose is once daily oral inhalation of Breo Ellipta 100 mcg/25 mcg.

## **3 REGULATORY HISTORY**

A REMS for Breo Ellipta was voluntarily submitted by GSK with NDA 204275 on July 12, 2012 to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

A Pulmonary and Allergy Advisory Committee was held on April 17, 2013 to discuss the safety and efficacy of this product. The panel members voted (9:4) in favor of Breo Ellipta efficacy, safety and approval.

## **4 MATERIALS REVIEWED**

- Proposed REMS for NDA 204275 received July 12, 2012
- Clinical review Breo Ellipta NDA 204275 by Sofia Chaudhry, M.D., dated March 18, 2013

## **5 BACKGROUND**

### **5.1 OVERVIEW OF CLINICAL PROGRAM**

The core development program to support efficacy of fluticasone furoate 100 mcg/ vilanterol 25 mcg per day consisted of the following four clinical trials (for details see clinical review by Sofia Chaudhry, M.D.):

- Studies HZC112206 and HZC112207: Randomized, double-blind, placebo controlled, 24-week, lung function trials
- Studies HZC102871 and HZC102970 were 52-week exacerbation trials

### **5.2 SAFETY CONCERNS**

The safety profile for fluticasone furoate 100 mcg/ vilanterol 25 mcg appears similar to the safety profile described for other ICS/LABA products for COPD. An increase in pneumonias related to the fluticasone furoate was observed; also seen was an increased risk of fractures associated with use of fluticasone furoate/vilanterol combination over

vilanterol alone. Most common adverse events included nasopharyngitis, headache, upper respiratory tract infection, and oral candidiasis.

A total of 11 deaths were reported from clinical trials. The clinical reviewer commented that given a relatively older and chronically sick population, deaths are not unexpected in a COPD development program. The most common SAE reported was COPD exacerbation followed by pneumonias; these are known risks in the underlying population and with use of inhaled corticosteroids with LABA in COPD.

## **6 RISK MANAGEMENT PROPOSED BY APPLICANT**

GSK voluntarily submitted a REMS for Breo Ellipta with the goals to inform prescribers of the increased risk of asthma related death and serious outcomes with the LABA and appropriate use of Breo Ellipta. The proposed REMS consists of a:

- Communication Plan that includes:
  - Dear Healthcare Professional Letter (DHCPL)
  - Printed or web-based information for healthcare providers
  - Dear Medical Society Letter
- A timetable for submission of REMS assessment annually from the date of the approval of the REMS.

## **7 DISCUSSION**

GSK voluntarily submitted a REMS for Breo Ellipta that was consistent with LABAs. The REMS for the LABAs was based on new safety information of asthma related deaths, intubations and hospitalizations with the use of the class of LABA. The LABA class REMS was eliminated after REMS Oversight Committee concurrence dated June 18, 2012 that a REMS for the LABAs was not required since the REMS assessments results demonstrated that information regarding LABA safety and asthma-related death has been widely distributed to physicians with demonstrated uptake of the information into clinical practice.

Review of NDA 204275 indicated that the risks of Breo Ellipta were similar to the approved LABA. No additional safety issues were identified and no asthma related deaths with Breo Ellipta were reported. The clinical reviewer is recommending approval of Breo Ellipta for once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). There are no planned postmarket requirements or commitments.

## **8 CONCLUSION**

DPARP and DRISK determined (discussions at the Mid Cycle Review) that the risks associated with Breo Ellipta can be managed at this time through labeling and routine pharmacovigilance and that a REMS for Breo Ellipta is not necessary to ensure the benefits outweigh the risks.

DRISK and DPARP are in agreement that a REMS for Breo Ellipta is not necessary at this time and that routine pharmacovigilance measures are acceptable.

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/s/  
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04/22/2013

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