

CENTER FOR DRUG EVALUATION AND
RESEARCH

APPLICATION NUMBER:

203108Orig1s000

RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)

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

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: July 30, 2014

Reviewer(s): Reema Mehta, Pharm.D., M.P.H., Acting Deputy Division
Director
Division of Risk Management

Acting Division Director Cynthia LaCivita, Pharm.D.
Division of Risk Management

Drug Name(s): Striverdi Respimat® (olodaterol)

Therapeutic Class: Long-acting beta₂-adrenergic agonist

Dosage and Route: Inhalation Spray; 2.5 mcg/actuation

Application Type/Number: NDA 203-108

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals Inc.

OSE RCM #: 2014-1188

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) re-evaluation of the need for a Risk Evaluation and Mitigation Strategy (REMS) for Striverdi Respimat[®] (olodaterol) inhalation spray, NDA 203-108, submitted by Boehringer Ingelheim Pharmaceuticals Inc. (BI). The initial NDA was received May 14, 2012 and included a REMS proposal that was comprised of a communication plan and timetable for submission of assessments. The NDA received a Complete Response (CR) Letter due to findings by the Office of Compliance that the manufacturing and testing facilities associated with the drug substance and drug product were out of compliance with relevant GMP requirements. The Applicant responded to the CR Letter as a NDA Resubmission Class I on June 2, 2014, this submission did not include a proposed REMS.

DRISK evaluated the proposed REMS during the first review cycle (DRISK REMS Review, February 15, 2013) and concluded that a REMS was not necessary for the product at that time.

1.1 BACKGROUND

Olodaterol is a long-acting beta-2 adrenergic agonist (LABA). The Applicant has proposed the following indication for Striverdi Respimat: for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Striverdi Respimat is not indicated to treat acute deteriorations of COPD or to treat asthma.

Striverdi Respimat consists of a Striverdi Respimat inhaler and an aluminum cylinder (Striverdi Respimat cartridge) containing olodaterol (as the hydrochloride). Each actuation from the Striverdi Respimat inhaler delivers 2.7 mcg olodaterol hydrochloride, equivalent to 2.5 mcg olodaterol. The recommended dose of Striverdi Respimat is two inhalations once-daily at the same time of the day.

BI submitted the original NDA for Striverdi Respimat with a proposed REMS consistent with the REMS that was required for the entire LABA class for the risk of asthma-related deaths, intubations, and hospitalizations associated with the use of LABAs. The Agency determined in 2012 that the REMS for LABAs were no longer required.

1.2 REGULATORY HISTORY

May 14, 2012: NDA 203-108 initially submitted for Striverdi Respimat. The NDA submission included a proposed REMS that included a CP and timetable for submission of assessments consistent with the REMS that was required for the entire LABA class (released 8/9/2012).

January 29, 2013: NDA was discussed at a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting. The PADAC voted 15 to 1 favoring approval as there was adequate clinical evidence of safety/efficacy.

March 14, 2013: NDA received a Complete Response (CR) Letter due to findings by the Office of Compliance that the manufacturing and testing facilities associated with the

drug substance and drug product were out of compliance with relevant GMP requirements.

June 2, 2014: Applicant responded to the CR Letter as a NDA Resubmission Class I.

2 MATERIALS REVIEWED

REMS Submission, May 14, 2012

Yasmin Chaudhry. DRISK REMS Review, February 15, 2013

Complete Response Letter, March 14, 2013

Robert Lim. Clinical Review, July 11, 2014

Package Insert Labeling, Submitted July 11, 2014

3 RESULTS OF REVIEW OF PROPOSED STRIVERDI RESPIMAT RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The core development program to support olodaterol 5 mcg once daily consisted of 3 dose ranging trials in COPD patients (1222.3, 1222.5, 1222.26), 4 dose ranging trials in asthma patients (1222.4, 1222.6, 1222.27, and 1222.29), 4 forty-eight week efficacy and safety trials (1222.11, 1222.12, 1222.13, 1222.14), 2 six week treatment period crossover exercise endurance trials (1222.37, 1222.38), and 4 six week treatment period crossover 24 hour spirometry trials (1222.24, 1222.25, 1222.39, 1222.40).

Support for efficacy is derived primarily from the four parallel group 48-week COPD trials, two of which were conducted primarily in the United States (US) and two of which were conducted primarily in Europe (EU). These trials shared the same spirometric co-primary endpoints of forced expiratory volume in 1 second (FEV1) AUC (0-3 hours) response and trough FEV1. The two US trials (1222.11 and 1222.12) were 3-arm trials which assessed the co-primary endpoints after 12 weeks of treatment. The two EU trials (1222.13 and 1222.14) were 4-arm trials including the active comparator formoterol and assessed the co-primary endpoints after 24 weeks. Trials 1222.13 and 1222.14 also included a third non-spirometric co-primary endpoint of Mahler Transitional Dyspnea Index (TDI) score assessed at 24 weeks and the key secondary endpoint of the Saint George's Respiratory Questionnaire (SGRQ).

These trials included a total of 3104 patients, 1759 of which were exposed to olodaterol (mean exposure approximately 300 days). The difference for olodaterol 5 mcg from placebo for FEV1 AUC (0-3 hours) response in trials 1222.11, 1222.12, 1222.13, and 1222.14 were 0.164, 0.134, 0.151, and 0.129L (all p-values <0.0001), respectively. For trough FEV1 response, the differences from placebo were 0.084 (p=0.0002), 0.033 (p>0.05), 0.078 (p=0.0002), and 0.053L (p=0.006), respectively.

3.2 SAFETY CONCERNS

The safety information for olodaterol 5 mcg comes primarily from the 48-week COPD trials. In the 48-week trials, 876 patients were exposed to olodaterol 5 mcg and 883 to olodaterol 10 mcg for a total of 1,759 exposed patients. An additional 1594 COPD

patients were exposed to olodaterol in shorter-term trials, for a total of 3353 COPD patients exposed for any duration during the olodaterol program. Of these patients, 1014 patients were exposed to olodaterol for ≥ 48 weeks (≥ 337 days). Five-hundred twelve (512) asthmatic patients were also exposed to oldodaterol during the development program.

There were a total of 53 on-treatment deaths in the 48-week trials (placebo=1.5%, olodaterol 5 mcg=1.5%, olodaterol 10 mcg=1.9%, and formoterol=2.2%). Based on adjudicated data, the most frequent cause of death was COPD exacerbation as expected in this patient population.

Serious adverse events (SAEs) were also evenly balanced among treatment groups, with 16.4% of placebo patients, 15.8% of olodaterol 5 mcg patients, 16.6% of olodaterol 10 mcg patients, and 15.0% of formoterol patients experiencing an SAE in the 48 week trials. As expected in this patient population, the most common SAEs were COPD exacerbation (5.8%), pneumonia (1.8%), all fractures (0.5%), and atrial fibrillation (0.5%). COPD exacerbations were evenly distributed across treatment groups. However, pneumonias were more common in the high-dose olodaterol groups (olodaterol 5 mcg=1.6%, olodaterol 10 mcg=2.5%) compared to placebo (1.5%). The same was true of atrial fibrillation (placebo=0.3%, olodaterol 5 mcg=0.6%, olodaterol 10 mcg=0.6%). An analysis of major cardiac events (MACE) was also conducted. This analysis demonstrated no imbalances.

3.3 APPLICANT'S PROPOSED REMS

The Applicant did not include a proposed REMS with the resubmission of this application. The Applicant's original submission consisted of a communication plan that outlined the same risks that were in the released LABA class REMS- to inform health care providers and prescribers of the risk of asthma related death with the use of LABA's, and their appropriate use.

4 DISCUSSION

Based on the results of the phase 3 pivotal trials, Striverdi Respimat demonstrated efficacy in the treatment of COPD. The safety profile observed in the clinical trials for Striverdi Respimat is consistent with the known safety profile for other LABAs.

BI submitted the original NDA for Striverdi Respimat with a proposed REMS consistent with the REMS that was required for the entire LABA class for the risk of asthma-related deaths, intubations, and hospitalizations associated with the use of LABAs. The Agency determined in 2012 that the REMS for LABAs were no longer required. The aforementioned class risk for LABAs is currently mitigated by a boxed warning in the prescribing information. The prescribing information for Stirverdi Respimat also contains the boxed warning for this risk.

DRISK original determination has not changed, a REMS is not as necessary to ensure the benefits of Striverdi Respimat outweigh the risks. There were no additional serious risks identified during the clinical trial program in the resubmission that are unique to Striverdi Respimat. Similar to the approved LABAs, the risks of Striverdi Respimat will be

communicated by the Prescribing Information.. DRISK had determined that a REMS is not necessary to ensure the benefits of Striverdi Respimat outweigh the risks.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not necessary for Striverdi Respimat. Striverdi Respimat has proven efficacy in the treatment of COPD patients. Based on the available data, the safety profile for Striverdi Respimat is consistent with the known safety profile for other LABAs. Thus, the benefit-risk profile for Striverdi Respimat is acceptable and the risks can be communicated through professional labeling.

Should DPARP have any concerns or questions, or if new safety information becomes available, please contact DRISK.

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/s/

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07/30/2014

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

Date: February 15, 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): Striverdi Respimat (olodaterol) oral inhalation solution

Dose: 5 mcg (2 inhalations of 2.5 mcg once a day)

Therapeutic Class: Long-acting beta₂-agonist (LABA)

Indication(s): Once daily-maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

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

Application Type/Number: NDA 203108

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals Inc.

OSE RCM #: 2012-1524

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a Risk Evaluation and Mitigation Strategy (REMS) for NDA 203108 Striverdi Respimat (olodaterol) oral inhalation solution is required.

Olodaterol is a new molecular entity that belongs to the class called long-acting beta-adrenergic agonists (LABA). The proposed indication is for once daily-maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The recommended dose is 5 mcg (2 inhalations of 2.5 mcg once daily). Olodaterol is formulated for use with the Respimat, a hand-held, pocket-sized, multi-dose, oral inhalation device.

A REMS for Olodaterol was voluntarily submitted by Boehringer Ingelheim on May 14, 2012 with NDA 203108 to the Division of Pulmonary, Allergy, and Rheumatology Products (DARP).

2 MATERIALS REVIEWED

- Proposed REMS for Striverdi (olodaterol) NDA 203108 received on May 14, 2012
- Clinical Review NDA 203108 Striverdi (olodaterol) by Robert H. Lim, M.D., dated January 17, 2013

3 BACKGROUND

3.1 OVERVIEW OF CLINICAL PROGRAM

The core development program¹ to support efficacy of olodaterol 5 mcg per day consisted of:

- Three dose ranging trials in COPD patients.
- Four dose ranging trials in asthma patients.
- Four 48-week efficacy and safety trials.
- Two 6-week treatment period crossover exercise endurance trials
- Four 6-week treatment period crossover 24-hour spirometry trials.

The nonclinical safety program for olodaterol was considered adequate to support the safety of the proposed clinical dose of 5 mcg/day.

Safety of olodaterol was evaluated from the 48-week trials in a total of 1,759 patients exposed to olodaterol. Fifty three deaths were reported in the 48-week trials; according to the clinical reviewer these were evenly split between the groups (placebo, formoterol and

¹ Clinical Review NDA 203108 Striverdi (olodaterol) by Robert H. Lim, M.D., dated January 17, 2013.

olodaterol) studied and the most frequent cause of death was COPD exacerbation as expected in this patient population. No asthma related deaths were reported. The most common serious adverse events were COPD exacerbation, pneumonia, fractures, and atrial fibrillation.

A Pulmonary-Allergy Drug Advisory Committee Meeting was held on January 29, 2013 to discuss the safety and efficacy of this product. The panel members voted (15:1) in favor of olodaterol bronchodilator efficacy, safety and approval.

The clinical reviewer is recommending approval of olodaterol for long-term, once daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). There are no planned postmarket requirements or commitments.

3.2 APPLICANT'S PROPOSED RISK MANAGEMENT PROGRAM

Boehringer Ingelheim Pharmaceuticals voluntarily submitted a proposed REMS with the goals to inform prescribers of the increased risk of asthma related death and serious outcomes with the LABA and appropriate use of olodaterol. The components of the proposed REMS include:

- 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.

4 DISCUSSION

Review of olodaterol indicated that the risks of olodaterol were similar to the approved LABA. Boehringer Ingelheim Pharmaceuticals voluntarily submitted a REMS 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 a decision was made on June 18, 2012 by the REMS Oversight Committee in conjunction with DPARP and DRISK that a REMS for the LABA was not required since the information regarding LABA safety and asthma-related death was widely distributed to physicians, and the results of the REMS assessments indicated that prescribers were aware of the risks of LABA and the new prescribing guidelines; additionally, no asthma related deaths were reported.

No additional safety issues were identified with olodaterol and no asthma related deaths with olodaterol were reported.

DPARP and DRISK determined that the risks associated with olodaterol can be managed at this time through labeling and routine pharmacovigilance and that a REMS for olodaterol is not necessary to ensure the benefits outweigh the risks.

5 CONCLUSION

DRISK and DPARP are in agreement that a REMS for Striverdi (olodaterol) is not necessary at this time and that routine pharmacovigilance measures are acceptable.

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/s/

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