

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206756Orig1s000

**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**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 2, 2015

Reviewer(s): Felicia Duffy, RN, BSN, MEd
Division of Risk Management

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Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Stiolto Respimat[®] (tiotropium bromide and olodaterol)

Therapeutic Class: Long-acting beta muscarinic agonist and long-acting beta₂-adrenergic agonist

Dosage and Route: Inhalation spray; 2.5 mcg/2.5 mcg per actuation

Indication: Long-term, once –daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema.

Application Type/Number: NDA 206756

Applicant/sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.

OSE RCM #: 2014-1150

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for Stiolto Respimat[®] (tiotropium bromide and olodaterol) inhalation spray, NDA 206756. On May 23, 2014, the Agency received an original NDA from Boehringer Ingelheim Pharmaceuticals Inc. (BI), for Stiolto Respimat as a fixed dose combination drug product intended as a once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The Applicant did not submit a proposed REMS for Stiolto Respimat.

1.1 PRODUCT BACKGROUND

Stiolto Respimat is a fixed dose combination product indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema.

Both monocomponents of Stiolto Respimat are approved and currently marketed in the United States (US).

Tiotropium (Tio) is a long-acting muscarinic antagonist (LAMA). Tiotropium bromide inhalation spray (Spiriva Respimat) was approved September 24, 2014 (NDA 021936). It is indicated for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including bronchitis and emphysema, and for reducing COPD exacerbations. It is available as a 2.5 mcg (equivalent to 3.124 mcg tiotropium bromide monohydrate) inhalation spray. Two actuations equal one dose.

Olodaterol (Olo) is a long-acting beta₂ adrenergic agonist (LABA). Olodaterol inhalation spray (Striverdi Respimat) was approved July 31, 2014 (NDA 203108) for long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is available as a 2.5 mcg (equivalent to 2.7 mcg olodaterol hydrochloride) inhalation spray. Two actuations equal one dose.

Stiolto Respimat consists of a Stiolto Respimat inhaler and an aluminum cylinder (Stiolto Respimat cartridge) containing a combination of tiotropium bromide (as the monohydrate) and olodaterol (as the hydrochloride). Each actuation delivers 3.124 mcg tiotropium bromide monohydrate (equivalent to 2.5 mcg Tio) and 2.736 mcg olodaterol hydrochloride (equivalent to 2.5 mcg Olo). The recommended dose of Stiolto Respimat is two inhalations once-daily at the same time of day.

1.2 REGULATORY HISTORY

On May 22, 2014, the Agency received an original NDA submission from BI for Stiolto Respimat for the maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The Applicant did not submit a proposed REMS.

The mid-cycle communication with the Applicant occurred on November 6, 2014. The Agency communicated to the Applicant that, at this time, no safety concerns have been identified that required a REMS to ensure safe use. The mid-cycle communication was finalized on December 5, 2014.

2 MATERIALS REVIEWED

- BI Original NDA 206756 submission for Stiolto Respimat. May 22, 2014
 - Section 2.5: Clinical Overview
 - Section 2.7: Clinical Summary
- BI Draft Package Insert Labeling, Submitted May 22, 2014
- BI Package Insert for Striverdi Respimat (Olodaterol), approved July 31, 2014
- BI Package Insert for Spiriva Respimat (Tiotropium), approved September 24, 2014
- Lim, R. MD. DPARP Mid-cycle Meeting Slides for NDA 206756, dated October 30, 2014
- Lim, R. MD. DPARP Draft Clinical Review for NDA 206756, dated December 19, 2014

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The core phase 3 COPD development program consisted of two replicate 52-week safety and efficacy trials (1237.5 and 1237.6), (b) (4) and one 6-week treatment period crossover 24-hour spirometry trial (1237.20).

The two replicate 52-week COPD trials were used as primary support of efficacy. These trials included 5-treatment arms which were as follows: Olo 5 mcg, Tio 2.5 mcg, Tio 5 mcg, Tio+Olo 2.5 mcg/5 mcg, and Tio+Olo 5 mcg/5 mcg. There were no placebo arms in these trials as there was sufficient evidence to support the efficacy of both Olo 5 mcg and Tio 5 mcg compared to placebo from the reference applications (see NDA 203108 and 021936). As such, demonstration of efficacy of the Tio+Olo FDC over their constituent monoproducts was sufficient to support efficacy for the FDC. The primary endpoints of these trials were trough forced expiratory volume in 1 second (FEV₁) and FEV₁ AUC (0-3hours) response at week 24. For both primary endpoints, both FDC doses demonstrated statistically significant improvements compared to both the constituent monotherapy products, demonstrating that both the Tio and Olo components of the FDC contributed to the treatment effect.

3.2 SAFETY CONCERNS

The safety information for Tio+Olo comes primarily from the 52-week COPD trials. The 52-week trials included a total of 5162 patients. Of these, 1029 received Tio+Olo 5 mcg/5 mcg and 1030 received Tio+Olo 2.5 mcg/5 mcg. The safety profile of the FDC was compared with their constituent monoproducts.

In the 52-week COPD trials there were a total of 75 deaths during the on-treatment period. The most common cause of death was COPD. This was true for the adjudicated and non-adjudicated analysis of death. The percentage of Tio+Olo 5 mcg/5 mcg patients that died (2%) was similar to that observed in the Olo 5 mcg group (1.7%) and lower than in the Tio 5 mcg group (2.2%).

Non-fatal serious adverse events (SAE) were generally similar between treatment groups, with 15.5% of Tio+Olo patients, 15.6% of Tio 5 mcg patients, and 16.6% of Olo 5 mcg patients experiencing a non-fatal SAE. The SAEs were slightly more frequent in the Tio+Olo 5 mcg/5 mcg group compared to both its monoproducts; however, the differences were relatively

small based on both percent and total number. The most common SAEs were COPD exacerbation (32.8%), nasopharyngitis (12.3%), upper respiratory infection (5.8%), cough (4.0%), and dyspnea (4.0%).

An analysis of major cardiac events (MACE) was also conducted. This analysis demonstrated no imbalances.

4 DISCUSSION

Based on the results of the Phase 3 pivotal trials, Tio+Olo demonstrated improved efficacy in the treatment of COPD as compared to its monotherapy components. The safety profile observed in the clinical trials for Tio+Olo is consistent with the known safety profile for Tio monotherapy and Olo monotherapy in a comparable study population for an identical indication. Spiriva Respimat and Striverdi Respimat are currently approved without a REMS to ensure the benefits outweigh the risks. Therefore, DRISK has determined that a REMS is not necessary to ensure the benefits of Tio+Olo outweigh the risks.

5 CONCLUSION

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

Should DPARP have any concerns or questions, feel that a REMS may be warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

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/s/

FELICIA DUFFY
02/02/2015

REEMA J MEHTA
02/02/2015
I concur.