CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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:	June 23, 2015
Reviewer(s):	Bob Pratt, Pharm.D. Division of Risk Management
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D. Division of Risk Management
Acting Deputy Division Director:	Reema Mehta, Pharm.D., M.P.H. Division of Risk Management
Subject:	Evaluation to determine if a REMS is necessary
Drug Name(s):	tiotropium bromide (Spiriva® Respimat®) Inhalation Spray
Therapeutic Class:	Antimuscarinic Agent
Dosage and Route:	2.5 mcg inhalation once daily
Indication:	Long-term, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids
Application Type/Number:	NDA 207070
Applicant/sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2014-1766

1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for tiotropium bromide (Spiriva® Respimat®) Inhalation Spray, NDA 207070. On August 15, 2014, the Agency received an original NDA from Boehringer Ingelheim for Spiriva Respimat for the long-term, once-daily, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids. Spiriva Respimat was approved under NDA 21936 on September 24, 2014, for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, and for reducing COPD exacerbations.

1.1 DISEASE BACKGROUND[1-4]

Asthma is a chronic disease of the lungs characterized by airway inflammation, bronchial hyperresponsiveness, and reversible airflow obstruction due to smooth muscle contraction. The interaction of these characteristics determines the clinical manifestations and severity, and the response to treatment. Typical signs and symptoms of asthma include intermittent dyspnea, cough, and wheezing. As of 2004, it was estimated that as many as 300 million people of all ages and all ethnic backgrounds suffer from asthma worldwide.

Asthma treatments are categorized by their roles in the overall management of the disease. Quick-acting β_2-adrenergic agonists by inhalation are the most effective bronchodilators for rapid reversal of airflow obstruction and relief of symptoms. Long-acting inhaled β_2 agonists (LABA) are potent bronchodilators that have sustained activity for more than 12 hours, however, the use of these agents without concomitant inhaled corticosteroid therapy results in unsuppressed airway inflammation and a relatively high rate of asthma exacerbations. Inhaled corticosteroids suppress airway inflammation, decrease bronchial hyperresponsiveness, improve symptoms, and result in fewer disease exacerbations. Other treatment options include oral leukotriene antagonists, which bring about bronchodilation and may be an alternative to inhaled corticosteroids in patients with mild asthma, and anti-IgE monoclonal antibody therapy, which inhibits allergic reactions in the airways and is indicated for patients with moderate to severe asthma that have not responded adequately to other treatments.

1.2 PRODUCT BACKGROUND

Tiotropium bromide is a long-acting, inhaled anticholinergic bronchodilator approved for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, and for reducing COPD exacerbations. The product is available as a dry powder formulation using the HandiHaler® inhaler device and as a mist formulation using the Respimat® inhaler device. The recommended dosage (b) (4) once-daily (systemic exposure is similar despite the difference in dosage). The Applicant is proposing the

[1] Liu M. Pathogenesis of asthma. In:UpToDate, Bochner BS and Hollingsworth H (Eds), UpToDate, Waltham, MA, 2015.
[2] Fanta CH. In:UpToDate, Barnes PJ, Bochner BS, and Hollingsworth H (Eds), UpToDate, Waltham, MA 2015.
[3] Masoli M, et al. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. Allergy 2004; 59:469-478.
[4] Fanta CH. Asthma. N Engl J Med 2009; 360:1002-1014.

use of Spiriva Respimat 2.5 [redacted] once-daily for the long-term, add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids.

1.3 REGULATORY HISTORY

On August 15, 2014, the Agency received an original NDA from Boehringer Ingelheim for Spiriva Respimat as add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids. The review classification for the application is Standard. The Applicant did not submit a proposed REMS.

Subsequent to the submission of NDA 207070, Spiriva Respimat was approved under NDA 21936 on September 24, 2014, for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, and for reducing COPD exacerbations.

On April 30, and May 8 and May 15, 2015, the Agency received submissions to NDA 207070 related to the product labeling and to Chemistry, Manufacturing and Controls that constituted major amendments to the application. The goal date was extended by three months to September 15, 2015.

2 MATERIALS REVIEWED

- Spiriva Respimat, Original NDA 207070 submission for tiotropium bromide inhalation spray, received August 15, 2014, (Serial No. 0000)
    - Section 2.5, Clinical Overview
- Slides from NDA 207070 Mid-Cycle Meeting, January 5, 2015
- Spiriva Respimat, Original NDA 207070 submission for tiotropium bromide inhalation spray, received May 15, 2015, (Serial No. 17)
    - Draft Prescribing Information
- Chin S., Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) Clinical Review, NDA 207070, dated May 21, 2015

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The Applicant completed six phase 3, randomized, double-blind, placebo controlled, parallel group studies (the primary objective of one of these studies was to evaluate long-term safety) in adults, and two similar studies in adolescents 12–17 years of age, in the treatment of persistent asthma that ranged from mild to severe. The combined study populations included 3,761 adults and 789 adolescents. Most studies compared Spiriva Respimat 5 mcg daily versus 2.5 mcg daily versus placebo. Patients received maintenance inhaled corticosteroid therapy; additional controller medications such as LABA or leukotriene modifiers were used depending on disease severity (for the purpose of the studies, corticosteroids and other controller treatments were synonymous with placebo). The primary efficacy endpoint was maximum FEV_1 within 3 hours post-dosing (FEV_1 peak $_{(0\text{-}3h)}$), which was assessed at Week 12, 24, or 52 depending on the study design. Additional endpoints included trough FEV_1 (which was a co-primary endpoint in some

studies); the time to first severe asthma exacerbation; and an asthma control questionnaire responder rate.

In summary, five of the phase 3 studies in adults and a 24-week study in adolescents demonstrated superiority of Spiriva Respimat 5 mcg daily over placebo in terms of lung function improvement. In the 12-week study in adolescents, lung function improvement was statistically significant with the 2.5 mcg daily dose but not the 5 mcg dose; the 2.5 mcg dose resulted in statistically significant improvement in the three adult studies and both adolescent studies where it was evaluated. Furthermore, in four of five studies where the two doses were compared, the 2.5 mcg dose response was consistently higher than the 5 mcg dose.

3.2 SAFETY CONCERNS

For the purpose of this review, serious adverse events (SAEs) associated with Spiriva Respimat are defined by the regulatory definition of a serious outcome, such as a life-threatening reaction or hospitalization (among other outcomes). Severe adverse events (AEs) were defined in the clinical studies as incapacitating or causing inability to work or to perform usual activities. Some of the results below are categorized by asthma severity or patient age, whereas other results are described in terms of the primary safety population, which included all parallel group Phase 3 and Phase 2 studies.

3.2.1 Serious Adverse Events

There were no fatal adverse events reported in the clinical development program.

- Nonfatal SAEs of any nature were reported in 37/456 patients (8.1%) in adults with severe asthma treated with Spiriva Respimat 5 mcg daily compared with 40/456 patients (8.8%) who received placebo. 'Asthma' was reported as the most common SAE, and occurred in 17 patients in the treatment group and 21 patients in the placebo group.
- In adults with moderate asthma, SAEs were reported in 23/1,036 patients (2.2%) treated with Spiriva Respimat (either 2.5 mcg or 5 mcg daily) compared with 14/523 patients (2.7%) in the placebo group and 11/541 patients (2.0%) in a group treated with the LABA salmeterol. 'Asthma' was reported in three patients in the placebo group as well as three in the groups treated with Spiriva Respimat.
- In the adult safety population, the proportion of patients experiencing an SAE in the 2.5 mcg daily, 5 mcg daily, and placebo groups was 2%, 4%, and 5%, respectively.
- In the studies of adolescents, SAEs were reported in 8/516 patients (1.6%) treated with Spiriva Respimat (either 2.5 mcg or 5 mcg daily) compared with 2/273 patients (0.7%) in the placebo group. 'Asthma' was the only SAE that was reported for >1 patient overall, and it occurred in two patients in the Spiriva Respimat 5 mcg treatment group.

3.2.2 Severe adverse events

In studies of adults with severe asthma, the proportion of patients experiencing severe AEs was approximately equal in comparing Spiriva Respimat 5 mcg daily (12.5%) with placebo (11.6%). In patients with moderate asthma, 4.2% of patients receiving 2.5–5 mcg daily of Spiriva Respimat experienced severe AEs compared with 2.7% of patients in the placebo group. In the studies of adolescents, 1.4% of those treated with Spiriva Respimat 2.5–5 mcg daily experienced severe AEs compared with 1.1% of patients in the placebo group. 'Asthma' was the most

commonly reported severe AE in the primary safety population, and it occurred at a slightly greater frequency in the placebo group compared with those treated with Spiriva Respimat.

3.2.3 Major Adverse Cardiovascular Events (MACE)

In the overall safety population, MACE endpoints were reported for a total of 9 patients [Spiriva Respimat 5 mcg, n=4 (0.2%); Spiriva Respimat 2.5 mcg, n=1 (0.1%); placebo, n=4 (0.3%)]. The reported MACE endpoints included 5 patients with stroke [Spiriva Respimat 5 mcg, n=2; placebo n=3] and 4 patients with adverse events in the Standardized MedDRA sub-query myocardial infarction (broad) [Spiriva Respimat 5 mcg, n=2; Spiriva Respimat 2.5 mcg, n=1; placebo n=1]. None of the events occurred in adolescent patients.

4 DISCUSSION

Based on the results of the phase 3 studies, Spiriva Respimat 2.5 mcg once-daily provides substantial efficacy for the long-term, add-on maintenance treatment of asthma in patients 12 years of age and older – (b) (4) No safety trends were identified and there were no clinically significant differences in the number or type of serious or severe adverse events between groups treated with Spiriva Respimat compared with placebo. Overall, there were nominally fewer SAEs overall and SAEs due to asthma in the Spiriva Respimat groups than in the placebo group. MACE events occurred at a very low frequency and there was no significant difference between active treatment and placebo.

The approved Spiriva Respimat labeling for the treatment of COPD describes class effect warnings for anticholinergic drugs that include the worsening of narrow angle glaucoma or urinary retention; additional labeled warnings include hypersensitivity reactions, paradoxical bronchospasm, use of the drug in moderate to severe renal impairment (the drug is predominantly renally excreted), and that Spiriva Respimat is not intended for the treatment of acute symptoms. These warnings will be retained in the labeling revised with the new asthma indication.

Spiriva Respimat is currently approved without a REMS to ensure the benefits outweigh the risks in the COPD population. DRISK does not recommend a REMS as necessary to ensure the benefits of Spiriva Respimat outweigh the risks in the maintenance treatment of asthma in patients who remain symptomatic on at least inhaled corticosteroids. The risks of Spiriva Respimat may be effectively communicated by the Prescribing Information.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Spiriva Respimat for the proposed asthma indication. Spiriva Respimat has shown efficacy as add-on therapy in the maintenance treatment of asthma in adults and adolescents. There are no serious or severe safety issues which warrant a boxed warning. Thus, the benefit-risk profile is acceptable and the risks can be mitigated through professional labeling.

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

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/s/

ROBERT G PRATT
06/23/2015

REEMA J MEHTA
06/23/2015
I concur.