Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	April 6, 2018
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Product Name:	Spiriva Respimat (tiotropium bromide)
Pediatric Labeling Approval Date:	September 15, 2015 (approval date for NDA 207070) February 15, 2017 (NDA 021936)
Application Type/Number:	NDA 207070, 021936
Applicant/Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
OSE RCM #:	2018-107

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EXECUTIVE SUMMARY

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports with a serious outcome for Spiriva Respimat (tiotropium bromide/ NDA 207070 and 021936) in pediatric patients.

Tiotropium bromide monohydrate, a long-acting antimuscarinic, is available in two formulations: an inhalation spray (Spiriva Respimat) for the treatment of asthma and chronic obstructive pulmonary disease (COPD) and a dry powder for inhalation (Spiriva HandiHaler) for the treatment of COPD. Whereas Spiriva Respimat is indicated for use in pediatric patients 12 years of age and older for the treatment of asthma, Spiriva HandiHaler is only indicated for use in adults for the treatment of COPD.

Spiriva Respimat was approved on September 24, 2014 (NDA 021936), at a dose of 5 µg/day, for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations, and on September 15, 2015 (NDA 207070), at a dose of 2.5 µg/day, for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older. This review was triggered by the approval of Spiriva Respimat in pediatric patients 12 years of age and older for the long-term, once-daily, maintenance treatment of asthma and the expansion of the indication to patients 6 to 11 years of age on February 15, 2017.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome (n=2) for tiotropium in the FDA Adverse Event Reporting System (FAERS) database from September 24, 2014 (U.S. approval date for NDA 021936) through February 15, 2018. For the purpose of this review, we searched the FAERS database for all reports with the product active ingredient *tiotropium*, which retrieved reports for Spiriva HandiHaler in addition to the product of interest, Spiriva Respimat. We did not retrieve any fatal cases with tiotropium.

We identified two pediatric cases with a serious outcome. One foreign case described a 10-year-old male who was initiated on double the recommended dose of Spiriva Respimat and four months later was hospitalized from the medication error; no adverse event resulting from the medication error was reported. The second case described a 1-month-old patient who was initiated on Spiriva HandiHaler (tiotropium bromide inhalation powder) and developed a lung neoplasm 12 years later. The safety and effectiveness of Spiriva HandiHaler in pediatric patients have not been established. It would be unlikely that an infant or young pediatric patient would have the coordination and inspiratory force required to effectively use a dry powder inhaler. Additionally, this case lacked detailed information on the lung tumor pathology or contributing risk factors such as family history to assess causality. Spontaneous adverse event reports have limited utility in analyzing adverse events with a very long latency, such as the development of cancer. Therefore, this singular case does not represent a new safety signal at this time. There is no evidence from these data that there are any new pediatric safety concerns with this drug and we will continue to monitor all adverse events associated with the use of tiotropium.

1 INTRODUCTION

This review evaluates postmarketing adverse event reports with a serious outcome in pediatric patients for Spiriva Respimat (tiotropium bromide/ NDA 207070 and 021936) inhalation spray. This review was triggered by the approval of Spiriva Respimat in pediatric patients 12 years of age and older for the long-term, once-daily, maintenance treatment of asthma and the expansion of the indication to patients 6 to 11 years of age on February 15, 2017.

1.1 PEDIATRIC REGULATORY HISTORY

Tiotropium bromide monohydrate, a long-acting antimuscarinic, is available in two formulations: an inhalation spray (Spiriva Respimat) for the treatment of asthma and chronic obstructive pulmonary disease (COPD) and a dry powder for inhalation (Spiriva HandiHaler) for the treatment of COPD. Whereas Spiriva Respimat is indicated for use in pediatric patients 12 years of age and older for the treatment of asthma, Spiriva HandiHaler is only indicated for use in adults for the treatment of COPD.

Spiriva Respimat was approved on September 24, 2014 (NDA 021936), at a dose of 5 µg/day, for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations, and on September 15, 2015 (NDA 207070), at a dose of 2.5 µg/day, for the long-term, once-daily, maintenance treatment of asthma in patients 12 years of age and older.

The following regulatory history was reproduced from Dr. Stacy Chin's (medical officer, Division of Pulmonary, Allergy, and Rheumatology Products) clinical review of efficacy supplement (NDA 021936/S-007) to extend the asthma indication to children 1 to 11 years of age for tiotropium.[1]

Summary of Presubmission Regulatory Activity Related to Submission

September 15, 2015

- Approval of Spiriva Respimat 2.5 µg once daily for the long-term maintenance treatment of asthma in patients 12 years of age and older
- Approval letter outlined two Pediatric Research Equity Act (PREA)-required studies:
  - 2953-1: Conduct a 12-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6 to 11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.
  - 2953-2: Conduct a 48-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6 to 11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.

October 19, 2015

- Boeringher Ingelheim (BI) submitted a Proposed Pediatric Study Request (PPSR) which included three studies in 6 to 11-year-old patients and one

study in 1 to 5-year-old patients; all but one study had already been completed with final study reports submitted to the Agency.

February 12, 2016

- The Agency issued a Written Request outlining the following studies
  - Study 1: An in vitro characterization study of the dose delivery from the Respimat inhaler with at least one U.S.-marketed spacer.
  - Study 2: A double-blind, randomized, parallel group, placebo-controlled, efficacy and safety study in children ages 6 to 11 years with asthma who are symptomatic despite maintenance therapy with a stable medium-dose inhaled corticosteroid (ICS) either alone or in combination with another controller medication (e.g., long-acting beta-agonist or leukotriene modifier). The duration must be at least 48 weeks, and the study must include at least two doses of tiotropium bromide inhalation solution.

February 15, 2017

- Expanded indication down to 6 years and older based on three clinical trials in patients 6 to 11 years; previously approved in 12 years and older. The indication was not expanded to patients aged 1 to less than 6 years of age because of insufficient evidence to support efficacy.

1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES

The Spiriva Respimat product labeling dated 2/2017[2] contains the following select safety information:

----------CONTRAINDICATIONS----------
Hypersensitivity to tiotropium, ipratropium, or any component of this product

----------WARNINGS AND PRECAUTIONS----------

- Not for acute use, i.e., not a rescue medication
- Immediate hypersensitivity reactions: Discontinue SPIRIVA RESPIMAT at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, urticaria, rash, bronchospasm, or anaphylaxis, occur.
- Paradoxical bronchospasm: Discontinue SPIRIVA RESPIMAT and consider other treatments if paradoxical bronchospasm occurs.
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs.
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patient to consult a physician immediately if this occurs.

----------ADVERSE REACTIONS----------
The most common adverse reactions in:

- COPD: (>3% incidence in the placebo-controlled trials with treatment durations of between 4 and 48 weeks) were pharyngitis, cough, dry mouth, and sinusitis.
- Asthma: (>2% incidence in the placebo-controlled trials with treatment durations of between 12 and 52 weeks) were pharyngitis, headache, bronchitis, and sinusitis in adults.

2 POSTMARKET ADVERSE EVENT REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The Division of Pharmacovigilance I (DPV-I) searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy	
Date of Search	February 15, 2018
Time Period of Search	September 24, 2014* - February 15, 2018
Search Type	Quick Query
Product Names†	Product Active Ingredient: tiotropium, tiotropium bromide, tiotropium bromide monohydrate
Search Parameters	All ages, all outcomes, worldwide

** U.S. approval date for Spiriva Respimat NDA 021936*
† FAERS limitation: searching by Product Active Ingredient captures reports with both Spiriva Respimat and Spiriva HandiHaler.

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from September 24, 2014 to February 15, 2018 with Tiotropium

	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	13484 (12618)	3774 (2918)	606 (466)
Pediatrics (0 - <17 years)	30‡ (29)	**2 (1)**	0 (0)

** May include duplicates and transplacental exposures, and have not been assessed for causality*
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ Nineteen of 30 reports occurred with Spiriva HandiHaler

2.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

There were no fatal pediatric adverse events cases with tiotropium from September 24, 2014 through February 15, 2018 in the FAERS database.

2.4 SUMMARY OF NON-FATAL SERIOUS PEDIATRIC ADVERSE EVENT CASES (N=2)

There were two serious cases of non-fatal pediatric adverse events with tiotropium. Cases in this section are categorized by Preferred Terms (PT) that best represent the reported adverse event(s). Preferred terms are then grouped by like terms and organized by System Organ Class. Summary of the narratives are found below.

2.4.1 Injury, poisoning and procedural complications (N=1)

Labeled Event: Overdose (non-serious), Unlabeled Event: Medication error (serious)

Medication error, Overdose (n=1), Case # 14495001, hospitalization, Egypt, 2018: A 10-year-old male was initiated on Spiriva Respimat 2.5 microgram, 2 inhalations daily for the treatment of asthma and on the same day experienced an overdose. The event was considered non-serious. The patient experienced a medication error four months later. The event was considered serious which led to hospitalization. Spiriva was continued

and was restarted at 2.5 microgram, 1 inhalation daily. Concomitant medication included beclomethasone and no concomitant diseases or past diseases were reported. The patient continued to take Spiriva as needed per physician recommendation.

Reviewer Comment: This foreign case suggests the patient was initiated on double the recommended dose of Spiriva Respimat (recommended total daily dose is 2.5 mcg), which resulted in a medication error and hospitalization four months later. The case contains limited information and does not report whether the patient experienced an adverse event as a result of the medication error. Section 10 Overdosage of the Spiriva Respimat product label states that high doses of tiotropium may lead to anticholinergic signs and symptoms and dry mouth/throat/nasal mucosa can occur in a dose-dependent manner. We are unable to assess if this patient experienced an adverse event, however the dose was decreased and the Spiriva was continued after hospitalization.

2.4.2 Neoplasms benign, malignant and unspecified (N=1)

Unlabeled Event: Lung neoplasm malignant

Lung neoplasm malignant (n=1), Case # 12661132, other serious important medical event, U.S., 2016: A non-healthcare professional reported that a 1-month-old female patient was treated with Spiriva HandiHaler, 18 mcg administered once daily via inhalation. The patient initiated treatment for an unknown indication and twelve years later had a lung tumor. The therapy and outcome of the event were not reported and Spiriva was continued. Concomitant medication included albuterol.

Reviewer Comment: This case described the unapproved use of Spiriva HandiHaler (tiotropium bromide dry powder for inhalation) in a pediatric patient. Spiriva HandiHaler is approved for the treatment of bronchospasm associated with COPD in adults.[2] The safety and effectiveness of Spiriva HandiHaler in pediatric patients have not been established; it would be unlikely that an infant or young pediatric patient would have the coordination and inspiratory force required to effectively use a dry powder inhaler (DPI).[3] Additionally, there are no adaptations for DPIs (such as a valved holding chamber and spacer) to aid in proper administration to young pediatric patients. This information suggests that the case may be inaccurate.

Also, this case lacked detailed information on the lung tumor pathology or contributing risk factors such as family history to assess causality. Although the case is coded with the PT Malignant lung neoplasm, there is no information in the case to determine whether the lung tumor was malignant or benign. Spontaneous adverse event reports have limited utility in analyzing adverse events with a very long latency, such as the development of cancer. We are unable to draw any conclusions from this singular case as multiple unknown factors could have contributed to the development of the tumor over the 12-year period and it is not feasible for the infant patient to have received the reported drug product.

3 DISCUSSION

There were no new pediatric safety signals and no deaths identified with tiotropium.

4 CONCLUSION

There is no evidence from these data that there are any new pediatric safety concerns with this drug at this time.

5 RECOMMENDATIONS

We will continue to monitor all adverse events associated with the use of tiotropium.

6 REFERENCES

1. Chin, Stacy MD. Clinical Review of Efficacy Supplement for Spiriva Respimat NDA 021936/S-007. January 18, 2017.

2. Spiriva Respimat Prescribing Information. Boehringer Ingelheim International GmbH. Ridgefield, CT. Revised February 2017.

3. Ahrens, Richard C. The Role of the MDI and DPI in Pediatric Patients: "Children Are Not Just Miniature Adults." Respiratory Care, Volume October 2005.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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/s/

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