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

Date:	December 3, 2018
Reviewers:	Dipti Kalra, RPh, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer (Pediatrician) DPV-I
Team Leader:	Lisa Harinstein, PharmD, Safety Evaluator Team Leader DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, MS, BCPS, Deputy Director DPV-I
Product Names:	AirDuo RespiClick (fluticasone propionate and salmeterol xinafoate) ArmonAir RespiClick (fluticasone propionate)
Pediatric Labeling Approval Date:	January 27, 2017
Application Type/Number:	NDA 208799, 208798
Applicant/Sponsor:	Teva Pharmaceutical Industries Ltd.
OSE RCM #:	2018-2267

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for AirDuo RespiClick (fluticasone propionate/salmeterol xinafoate inhalation powder) and ArmonAir RespiClick (fluticasone propionate) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with AirDuo RespiClick and ArmonAir RespiClick in pediatric patients less than 17 years of age.

ArmonAir RespiClick (fluticasone propionate, NDA 208798) and AirDuo RespiClick (fluticasone propionate/salmeterol xinafoate inhalation powder, NDA 208799) are multidose dry powder inhalers (MDPI) approved by FDA on January 27, 2017, for the treatment of asthma in patients 12 years of age and older; the safety and effectiveness of both products have not been established in pediatric patients less than 12 years of age. Both MDPIs contain fluticasone propionate, an inhaled corticosteroid (ICS), but AirDuo RespiClick also contains a long-acting beta agonist (LABA), salmeterol xinafoate, in combination with fluticasone.

The safety profile for inhaled fluticasone propionate and salmeterol in patients with asthma has been well established, as both ingredients have been marketed for the treatment of asthma in other inhalation products (e.g., Flovent Diskus, Advair Diskus). Additionally, other ICSs and ICS/LABA combination products have been available in the U.S. for many years, including some ICSs since 1987.

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for AirDuo RespiClick and ArmonAir RespiClick in the FAERS database from January 27, 2017 (U.S. approval date) to October 1, 2018. We did not identify any fatal pediatric adverse event cases. Our FAERS search retrieved zero serious pediatric cases from January 27, 2017, to October 1, 2018.

There is no evidence from this 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 AirDuo RespiClick and ArmonAir RespiClick.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for AirDuo RespiClick (fluticasone propionate/salmeterol xinafoate inhalation powder) and ArmonAir RespiClick (fluticasone propionate) in pediatric patients less than 17 years of age. The Division of Pharmacovigilance I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with AirDuo RespiClick and ArmonAir RespiClick in pediatric patients less than 17 years of age.

1.1 PEDIATRIC REGULATORY HISTORY

ArmonAir RespiClick (fluticasone propionate, NDA 208798) and AirDuo RespiClick (fluticasone propionate/salmeterol xinafoate inhalation powder, NDA 208799) are multidose dry powder inhalers (MDPI) approved by FDA on January 27, 2017, for the treatment of asthma in patients 12 years of age and older.[1,2,3] Both MDPIs contain fluticasone propionate, an inhaled corticosteroid (ICS), but AirDuo RespiClick also contains a long-acting beta agonist (LABA), salmeterol xinafoate, in combination with fluticasone.

The safety profile for inhaled fluticasone propionate and salmeterol in patients with asthma has been well established, as both ingredients have been marketed for the treatment of asthma in other inhalation products (e.g., Flovent Diskus, Advair Diskus). Additionally, other ICSs and ICS/LABA combination products have been available in the U.S. for many years, including some ICSs since 1987.

The pediatric safety of Advair HFA Inhalation Aerosol, another inhalation product containing fluticasone propionate and salmeterol xinafoate, was presented at the Pediatric Advisory Committee Meeting on March 24, 2015. No new safety signals were identified in the Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review.[4]

1.2 RELEVANT LABELED SAFETY INFORMATION

The labeling for AirDuo RespiClick and ArmonAir RespiClick contain similar safety highlights. AirDuo RespiClick contains additional safety information, some of which pertains to the LABA component of the product. Select safety highlights that appear in both the AirDuo RespiClick product label dated March 2018 and ArmonAir RespiClick product label dated March 2018 are listed below:

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

- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma.
- Localized infections: *Candida albicans* infection of the mouth and pharynx may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk.
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, parasitic infection, or ocular herpes simplex. Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to AirDuo RespiClick or ArmonAir RespiClick.
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue AirDuo RespiClick or ArmonAir RespiClick slowly.
- Paradoxical bronchospasm: Discontinue AirDuo RespiClick or ArmonAir RespiClick and institute alternative therapy if paradoxical bronchospasm occurs.
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta adrenergic stimulation.
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content.
- Monitor growth of pediatric patients.
- Close monitoring for glaucoma and cataracts is warranted.

Select safety highlights unique to the AirDuo RespiClick product label are listed below:

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

- LABA monotherapy increases the risk of serious asthma-related events.
- Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia.
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis.
- Do not use in combination with an additional medicine containing LABA because of risk of overdose.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategies described in Table 1.

Table 1. FAERS Search Strategies*	
Search 1	
Date of Search	October 2, 2018
Time Period of Search	January 27, 2017† - October 1, 2018
Search Type	Quick Query
Product Terms	Product Name: AirDuo RespiClick NDA: 208799
Search Parameters	All ages, all outcomes, worldwide
Search 2	
Date of Search	October 2, 2018
Time Period of Search	January 27, 2017† - October 1, 2018
Search Type	Quick Query
Product Terms	Product Name: ArmonAir RespiClick NDA: 208798
Search Parameters	All ages, all outcomes, worldwide
* See Appendix A for a description of the FAERS database. † U.S. Approval date	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Tables 2 and 3 below present the number of adult and pediatric FAERS reports from January 27, 2017, to October 1, 2018, with AirDuo RespiClick and ArmonAir RespiClick, respectively.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from January 27, 2017, to October 1, 2018, with AirDuo RespiClick

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	7 (7)	2 (2)	0 (0)
Pediatrics (0 - <17 years)	4 (4)‡	**0 (0)**	0 (0)

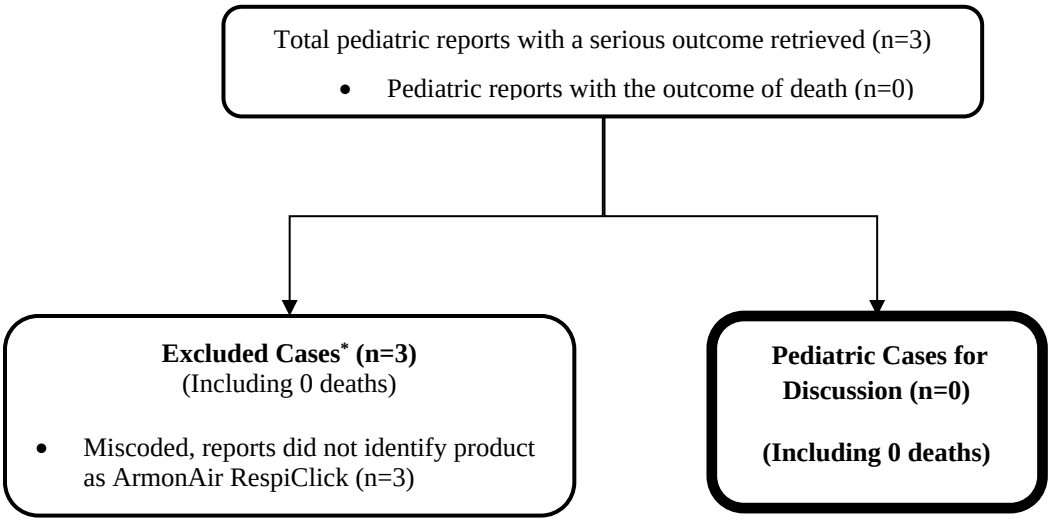
* May include duplicates and transplacental exposures, and have not been assessed for causality
† For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ We reviewed the four nonserious reports and did not identify any new signals. Air Duo RespiClick was prescribed in patients below the approved age in all four reports. Of the four reports, two did not contain an adverse event. The remaining two reports described an 11-year-old (unknown sex) who experienced nightmares two weeks after starting AirDuo RespiClick and a 6-year-old male who "doesn't feel like he is getting the dose."

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from January 27, 2017, to October 1, 2018, with ArmonAir RespiClick

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	12 (1)	12 (1)	0 (0)
Pediatrics (0 - <17 years)	3 (2)	**3‡(2)**	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.
‡ See Figure 1. Selection of Serious Pediatric Cases with ArmonAir RespiClick.

Figure 1. Selection of Serious Pediatric Cases with ArmonAir RespiClick



3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved zero serious pediatric cases for AirDuo RespiClick and ArmonAir RespiClick from January 27, 2017, to October 1, 2018. We did not identify any fatal pediatric adverse event cases with either product.

4 DISCUSSION

We did not identify any serious or fatal pediatric cases with AirDuo RespiClick or ArmonAir RespiClick at this time.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns for AirDuo RespiClick or ArmonAir RespiClick at this time.

6 RECOMMENDATION

DPV-I recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of AirDuo RespiClick and ArmonAir RespiClick.

7 REFERENCES

1. AirDuo RespiClick Prescribing Information. Teva Respiratory, LLC. Frazer, PA. Revised March 2018.
2. ArmonAir RespiClick Prescribing Information. Teva Respiratory, LLC. Frazer, PA. Revised March 2018.
3. He L, Marathe, A. ArmonAir RespiClick and AirDuo RespiClick Office of Clinical Pharmacology Integrated Review. October 28, 2016.
4. Kalra, D, Pham T. Advair HFA Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. January 15, 2015.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIPTI KALRA
12/03/2018

IVONE E KIM
12/03/2018

LISA M HARINSTEIN
12/04/2018

MONICA MUNOZ
12/04/2018