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 Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date: April 22, 2025

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Product Name	Application	Applicant	Pediatric Labeling Date
ArmonAir Respiclick (fluticasone propionate) inhalation powder, ArmonAir Digihaler (fluticasone propionate) inhalation powder	NDA 208798	Teva Pharmaceutical Industries Ltd	7/9/2021
AirDuo Respiclick (fluticasone propionate/salmeterol xinafoate) inhalation powder, AirDuo Digihaler (fluticasone propionate/salmeterol xinafoate) inhalation powder	NDA 208799	Teva Pharmaceutical Industries Ltd	7/9/2021

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ArmonAir (fluticasone propionate) inhalation powder and AirDuo (fluticasone propionate/salmeterol xinafoate) inhalation powder in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ArmonAir and AirDuo in pediatric patients.

ArmonAir (fluticasone propionate) inhalation powder for oral inhalation use is a corticosteroid first approved in the U.S. on January 27, 2017, for maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older. On July 9, 2021, the FDA approved expanding the ArmonAir indication to include use as the maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older. Of note, ArmonAir has been discontinued from marketing.

AirDuo (fluticasone propionate and salmeterol) inhalation powder for oral inhalation use is a combination of a corticosteroid and a long-acting beta2-adrenergic agonist (LABA) that was initially approved in the U.S. on January 27, 2017. AirDuo is currently indicated for treatment of asthma in adult and pediatric patients aged 12 years and older. AirDuo should be used for patients not adequately controlled on long term asthma control medication such as an inhaled corticosteroid or whose disease warrants initiation of treatment with both an inhaled corticosteroid and LABA. AirDuo is not indicated for the relief of acute bronchospasm. On July 9, 2021, the AirDuo labeling was updated to include information from clinical trials that failed to establish safety and effectiveness for AirDuo for the treatment of asthma in patients younger than 12 years of age.

This pediatric postmarketing pharmacovigilance review for ArmonAir and AirDuo was prompted by their respective labeling updates on July 9, 2021.

DPV reviewed all U.S. serious FAERS reports with ArmonAir and AirDuo in pediatric patients less than 18 years of age from October 2, 2018 – February 11, 2025, and identified six reports for ArmonAir and zero reports with AirDuo; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with ArmonAir or AirDuo in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for ArmonAir or AirDuo at this time and will continue routine pharmacovigilance monitoring for ArmonAir and AirDuo.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for ArmonAir (fluticasone propionate) inhalation powder and AirDuo (fluticasone propionate/salmeterol xinafoate) inhalation powder in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ArmonAir and AirDuo in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

ArmonAir[a] (fluticasone propionate) inhalation powder for oral inhalation use is a corticosteroid first approved in the U.S. on January 27, 2017, for maintenance treatment of asthma as prophylactic therapy in patients aged 12 years and older.[1] On July 9, 2021, the FDA approved expanding the ArmonAir indication to include use as the maintenance treatment of asthma as prophylactic therapy in patients aged 4 years and older.[2] Of note, ArmonAir has been discontinued from marketing.[3]

AirDuo[b] (fluticasone propionate and salmeterol) inhalation powder for oral inhalation use is a combination of a corticosteroid and a long-acting beta2-adrenergic agonist (LABA) that was initially approved in the U.S. on January 27, 2017.[4] AirDuo is currently indicated for treatment of asthma in adult and pediatric patients aged 12 years and older.[5] AirDuo should be used for patients not adequately controlled on long term asthma control medication such as an inhaled corticosteroid or whose disease warrants initiation of treatment with both an inhaled corticosteroid and LABA.[5] AirDuo is not indicated for the relief of acute bronchospasm. On July 9, 2021, the AirDuo labeling was updated to include information from clinical trials that failed to establish safety and effectiveness for AirDuo for the treatment of asthma in patients younger than 12 years of age.[6]

This pediatric postmarketing pharmacovigilance review for ArmonAir and AirDuo was prompted by their respective labeling updates on July 9, 2021.

FDA previously presented pediatric postmarketing pharmacovigilance reviews for fluticasone products for oral inhalation use to the Pediatric Advisory Committee (PAC). On January 15, 2015, the Office of Surveillance and Epidemiology (OSE) performed a review of postmarket adverse event reports with serious outcomes for Advair HFA (fluticasone propionate/salmeterol xinafoate inhalation aerosol). OSE's review did not identify any new safety concerns and recommended return to routine monitoring for adverse events with fluticasone

[a] ArmonAir was available as a Respiclick and Digihaler inhaler under NDA 208798. Both Respiclick and Digihaler were breath-activated, dry powder inhalers. The Digihaler contained a built-in electronic module allowing for the capture, storage and sharing of product use data via mobile App whereas Respiclick did not have built-in sensors or data-sharing capabilities. ArmonAir Respiclick and ArmonAir Digihaler were available in the same strengths and had the same indication. The Applicant for ArmonAir discontinued marketing for both Respiclick and Digihaler.
[b] AirDuo was available as a Respiclick and Digihaler inhaler under NDA 208799. Both Respiclick and Digihaler were breath-activated, dry powder inhalers. The Digihaler contained a built-in electronic module allowing for the capture, storage and sharing of product use data via mobile App whereas Respiclick did not have built-in sensors or data-sharing capabilities. AirDuo Respiclick and Digihaler were available in the same strengths and had the same indication The Applicant for AirDuo discontinued marketing of all strengths of the Digihaler as of April 30, 2024. AirDuo Respiclick remains available.

propionate/salmeterol xinafoate. OSE's evaluation was presented to the PAC on March 24, 2015.[7] On December 3, 2018, DPV completed a review of postmarket adverse event reports with serious outcomes for ArmonAir and AirDuo in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with ArmonAir and AirDuo. DPV's evaluation was presented to the PAC on March 28, 2019, via webposting.[8]

1.2 RELEVANT LABELED SAFETY INFORMATION

The ArmonAir and AirDuo respective labeling contain the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional ArmonAir and AirDuo labeling information, please refer to the full prescribing information.

ArmonAir Labeling:[5]

_____ CONTRAINDICATIONS _____

- Primary treatment of status asthmaticus or other acute episodes of asthma requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or any ingredients of ArmonAir Digihaler. (4)

_____ WARNINGS AND PRECAUTIONS _____

- Localized infections: Candida albicans infection of the mouth and throat may occur. Monitor patients periodically. Advise the patient to rinse his/her mouth with water without swallowing after inhalation. (5.1)
- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, parasitic infections 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. (5.3)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to ArmonAir Digihaler. (5.4)
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue ArmonAir Digihaler slowly. (5.5)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.7)
- Monitor growth of pediatric patients. (5.8)
- Close monitoring for glaucoma and cataracts is warranted. (5.9)
- Paradoxical bronchospasm: Discontinue ArmonAir Digihaler and institute alternative therapy if paradoxical bronchospasm occurs. (5.10)

_____ ADVERSE REACTIONS _____

Most common adverse reactions (greater than or equal to 3%): upper respiratory tract infection, nasopharyngitis, oral candidiasis, headache, and cough. (6.1)

8.4 Pediatric Use

The safety and effectiveness of ArmonAir Digihaler in the maintenance treatment of asthma as prophylactic therapy in pediatric patients 4 years of age and older have been established.

Use of ArmonAir Digihaler for this indication in adolescents ages 12 to 17 years is supported by evidence from two adequate and well-controlled trials in adult and adolescent patients 12 years old and older with persistent symptomatic asthma despite ICS or ICS/LABA therapy (Trials 1 and 2) [see Clinical Studies (14.2)]. In these trials, 50 adolescents received fluticasone propionate MDPI one inhalation twice daily.

Use of ArmonAir Digihaler for this indication in pediatric patients aged 4 to 11 years is supported by evidence from one adequate and well-controlled trial of fluticasone propionate MDPI (Trial 3) [see Clinical Studies (14.2)]. In this trial, 419 pediatric patients received fluticasone propionate MDPI 30 mcg or 55 mcg one inhalation twice daily.

The safety and effectiveness of ArmonAir Digihaler in patients below the age of 4 years have not been established.

Effect on Growth

Inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth velocity when administered to pediatric patients [see Warnings and Precautions (5.8)]. A reduction of growth velocity in children or teenagers may occur as a result of poorly controlled asthma or from use of corticosteroids, including inhaled corticosteroids. The effects of long-term treatment of children and adolescents with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known.

AirDuo Labeling:[6]

----------CONTRAINDICATIONS----------

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4)
- Severe hypersensitivity to milk proteins or any ingredients of AIRDUO RESPICLICK. (4)

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

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Deterioration of asthma and acute episodes: Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- Do not use in combination with an additional medicine containing LABA because of risk of overdose. (5.3)
- 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. (5.4)
- 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. (5.5)
- 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. (5.6)
- 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 slowly. (5.7)
- Paradoxical bronchospasm: Discontinue AIRDUO RESPICLICK and institute alternative therapy if paradoxical bronchospasm occurs. (5.9)
- Use with caution in patients with cardiovascular or central nervous system disorders because of beta adrenergic stimulation. (5.11)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.12)
- Monitor growth of pediatric patients. (5.13)
- Close monitoring for glaucoma and cataracts is warranted. (5.14)
- Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia. (5.15, 5.17)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.16)

----------ADVERSE REACTIONS ----------

Most common adverse reactions (greater than or equal to 3%): nasopharyngitis, oral candidiasis, headache, cough and back pain. (6.1)

8.4 Pediatric Use

The safety and effectiveness of AIRDUO RESPICLICK have been established for the treatment of asthma in pediatric patients aged 12 years and older whose asthma (1) is inadequately controlled on a long term asthma control medication or (2) warrants initiation of treatment with both an ICS and a LABA.

Use of AIRDUO RESPICLICK in pediatric patients aged 12 to 17 years for this indication is supported by evidence from two adequate and well-controlled trials in pediatric patients 12 years old and older with persistent symptomatic asthma despite ICS or ICS/LABA therapy (Trials 1 and 2) [see Clinical Studies (14)]. In these trials, 58 adolescents received AIRDUO RESPICLICK one inhalation twice daily.

The safety and effectiveness of AIRDUO RESPICLICK have not been established in pediatric patients younger than 12 years of age for the treatment of asthma. Effectiveness was not demonstrated in one adequate and well-controlled study conducted in 211 patients aged 4 to 11 years with persistent asthma on a stable asthma regimen who were treated with AIRDUO RESPICLICK 55 mcg/14 mcg one inhalation twice daily.

Effect on Growth

Inhaled corticosteroids, including fluticasone propionate, a component of AIRDUO RESPICLICK, may cause a reduction in growth velocity in adolescents [see Warning and Precautions (5.13)]. The growth of pediatric patients receiving ICS, including AIRDUO RESPICLICK, should be monitored.

If an adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect of corticosteroids should be considered. In such patients, the potential growth effects of prolonged ICS treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of ICS, including AIRDUO

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	February 12, 2025
Time period of search	October 2, 2018† - February 11, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Search 1 Product name: ArmonAir Digihaler, ArmonAir Respiclick Case application number: NDA208798
	Search 2 Product name: AirDuo Digihaler, AirDuo Respiclick Case application number: NDA208799
MedDRA search terms (Version 27.1)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious Country Derived: USA
* See Appendix A for a description of the FAERS database. † Data lock date from last DPV pediatric postmarketing pharmacovigilance review for ArmonAir and AirDuo. ‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; USA=United States of America	

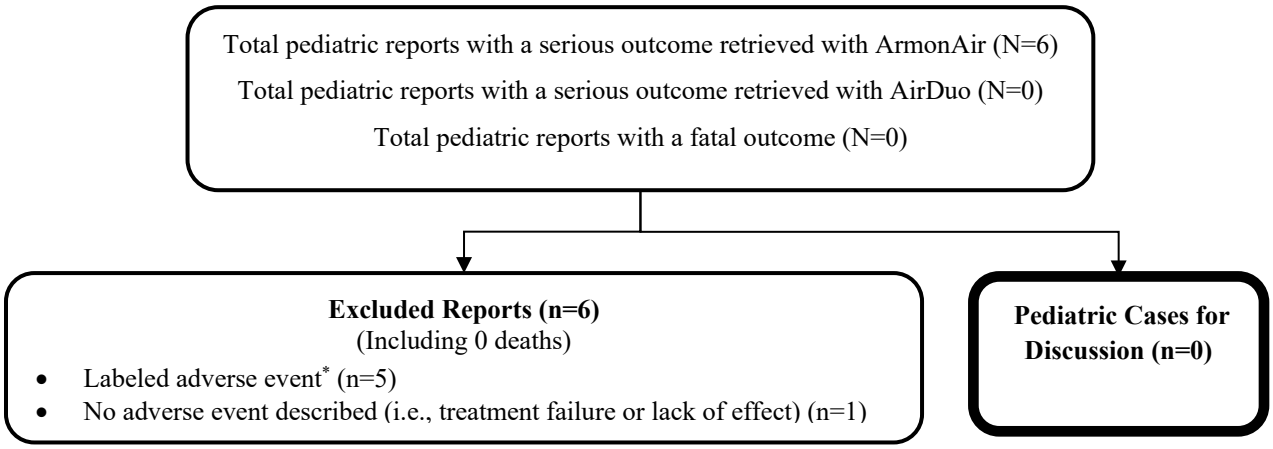
3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved six U.S. serious pediatric reports for ArmonAir and zero U.S. serious pediatric reports for AirDuo for patients less than 18 years old from October 2, 2018 – February 11, 2025. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all six reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With ArmonAir or AirDuo



* Labeled adverse event does not represent increased severity.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with ArmonAir and AirDuo in pediatric patients less than 18 years of age from October 2, 2018 – February 11, 2025, and identified six reports for ArmonAir and zero reports with AirDuo; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with ArmonAir or AirDuo in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for ArmonAir or AirDuo at this time and will continue routine pharmacovigilance monitoring for ArmonAir and AirDuo.

6 REFERENCES

1. ArmonAir Respiclick (fluticasone propionate) inhalation powder. [Prescribing information]. Frazer, PA; Teva Respiratory, LLC: January 2017.
2. ArmonAir Digihaler (fluticasone propionate) inhalation powder. [Prescribing information]. Parsippany, NJ; Teva Respiratory, LLC: July 2021.
3. ArmonAir Digihaler. NDA 208798. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208798
4. AirDuo Respiclick (fluticasone propionate and salmeterol) inhalation powder. [Prescribing information]. Frazer, PA; Teva Respiratory, LLC: January 2017.
5. ArmonAir Digihaler (fluticasone propionate) inhalation powder. [Prescribing information]. Parsippany, NJ; Teva Respiratory, LLC: April 2022.
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7. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. NDA 021254. January 15, 2015. Available at: https://wayback.archive-it.org/7993/20180127092530/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM437394.pdf
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7 APPENDICES

7.1 APPENDIX A. 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 FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.