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:	October 25, 2022
Safety Evaluator:	Omayma Kishk, PharmD, BCPPS Division of Pharmacovigilance-I (DPV-I)
Medical Officer:	Ivone Kim, MD DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, PhD DPV-I
Product Name:	Arnuity Ellipta (fluticasone furoate)
Pediatric Labeling Approval Date:	May 17, 2018
Application Type/Number:	NDA 205625
Applicant:	GlaxoSmithKline
TTT Record ID:	2022-1729

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Arnuity Ellipta (fluticasone furoate inhalation powder) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Arnuity Ellipta in pediatric patients.

Arnuity Ellipta is an inhaled corticosteroid approved in the U.S. on August 20, 2014, for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. On May 17, 2018, FDA extended the indication for Arnuity Ellipta to include once-daily maintenance treatment of asthma as prophylactic therapy in pediatric patients ages 5 through 11 years of age.

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change for Arnuity Ellipta on May 17, 2018.

DPV reviewed all U.S. serious FAERS reports with Arnuity Ellipta in the pediatric population (ages 0 – 16 years) from February 15, 2017, through September 15, 2022. We identified a singular case reporting an unlabeled event of tics. The case lacked clinical information and additional evaluation of the FAERS database and medical literature did not identify sufficient evidence to support a signal. We identified no new safety signals and no deaths directly associated with Arnuity Ellipta.

DPV will continue to monitor all adverse events associated with the use of Arnuity Ellipta.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Arnuity Ellipta (fluticasone furoate inhalation powder) in pediatric patients through age 16 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with Arnuity Ellipta in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Arnuity Ellipta is an inhaled corticosteroid approved in the U.S. on August 20, 2014, for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. On May 17, 2018, FDA extended the indication for Arnuity Ellipta to include once-daily maintenance treatment of asthma as prophylactic therapy in pediatric patients ages 5 through 11 years of age. A summary of the study design and findings are summarized below from the Arnuity Ellipta Clinical Review.[1]

> "The primary data for this review is derived from Study HZA106855, a well-controlled study assessing the efficacy of Arnuity Ellipta in 596 children ages 5 to 11 years with uncontrolled asthma. Clinically and statistically significant improvements were observed over weeks 1 through 12 compared with placebo in morning PEF for all three doses of Arnuity Ellipta investigated (Arnuity Ellipta 25 mcg, 50 mcg, and 100 mcg once daily).
>
> Studies HZA107112 and HZA107118 assessed the pharmacodynamic effects of Arnuity Ellipta on short-term lower leg growth and HPA axis suppression, respectively.
>
> Review of the studies did not demonstrate clinically significate changes in either assessment in Arnuity Ellipta treated subject compared to placebo-treated subjects.
>
> Review of the safety database, which consisted of 817 subjects, demonstrated that the incidence of adverse events (AE) was low across all five studies with no apparent dose-response effect. There were no deaths and only a total of two serious adverse events (SAE) in Arnuity-treated subjects both of whom made a full recovery. The types and frequencies of common AEs were similar to that reported in the current Arnuity Ellipta USPI and no new safety signals were identified. Review of the 120-day safety update was consistent with the data presented in the initial submission and no new safety signals were identified."

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change for Arnuity Ellipta on May 17, 2018. The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Arnuity Ellipta in pediatric patients. OSE's evaluation, dated May 22, 2017, was prompted by the approval of Arnuity Ellipta on August 20, 2014. OSE's evaluation did not identify any new safety concerns and resulted in recommendations to return to routine monitoring for adverse events with Arnuity Ellipta.[2]

Reference ID: 5066063

1.2 RELEVANT LABELED SAFETY INFORMATION

The Arnuity Ellipta labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[3] For further labeling information, please refer to the full prescribing information.

---------- **CONTRAINDICATIONS** ----------

- Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. (4.1)
- Severe hypersensitivity to milk proteins or any ingredients. (4.2)

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

- *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. (5.1)

- Do not use for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)
- Potential worsening of infections (e.g., existing tuberculosis; fungal, bacterial, viral, or parasitic infections; 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)
- Risk of impaired adrenal function when transferring from systemic corticosteroids. Wean patients slowly from systemic corticosteroids if transferring to ARNUITY ELLIPTA. (5.4)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, consider appropriate therapy. (5.5)
- If paradoxical bronchospasm occurs, discontinue ARNUITY ELLIPTA and institute alternative therapy. (5.7)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.9)
- Monitor growth of children and adolescent patients. (5.10)
- Glaucoma and cataracts may occur with long-term use of inhaled corticosteroids. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use ARNUITY ELLIPTA long term. (5.11)

---------- **ADVERSE REACTIONS** ----------

Most common adverse reactions reported in ≥5% of adult and adolescent subjects are nasopharyngitis, bronchitis, upper respiratory tract infection, and headache. (6.1)

Most common adverse reactions reported in ≥3% of pediatric subjects aged 5 to 11 years are pharyngitis, bronchitis, and viral infection. (6.1)

Reference ID: 5066063

8.4 Pediatric Use

The safety and efficacy of ARNUITY ELLIPTA in pediatric patients with asthma aged 5 to 11 years have been established in 3 clinical trials. In those trials, 234 subjects were administered ARNUITY ELLIPTA 50 mcg once daily. Subjects aged 5 to 11 years demonstrated safety and efficacy results similar to those observed in subjects aged 12 years and older. The safety and efficacy of ARNUITY ELLIPTA have not been established in pediatric patients aged younger than 5 years. *[See Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.2), Clinical Studies (14.2).]*

Effects on Growth

Orally inhaled corticosteroids may cause a reduction in growth velocity when administered to children and adolescents. A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids, including ICS. The effects of long-term treatment of children and adolescents with ICS, including fluticasone furoate, on final adult height are not known.

Controlled clinical trials have shown that ICS may cause a reduction in growth in children. In these trials, the mean reduction in growth velocity was approximately 1 cm/year (range: 0.3 to 1.8 cm/year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving orally inhaled corticosteroids, including ARNUITY ELLIPTA, should be monitored routinely (e.g., via stadiometry). The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including ARNUITY ELLIPTA, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A randomized, double-blind, parallel-group, multicenter, 1-year, placebo-controlled trial evaluated the effect of once-daily treatment with 110 mcg of fluticasone furoate in the nasal spray formulation on growth velocity assessed by stadiometry. The systemic exposure of fluticasone furoate in this trial is lower than that of ARNUITY ELLIPTA 50 mcg. The subjects were 474 prepubescent children (girls aged 5 to 7.5 years and boys aged 5 to 8.5 years). Mean growth velocity over the 52-week treatment period was lower in the subjects receiving fluticasone furoate nasal spray (5.19 cm/year) compared with placebo (5.46 cm/year). The mean reduction in growth velocity was 0.27 cm/year (95% CI: 0.06, 0.48) *[see Warnings and Precautions (5.10)]*.

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	September 16, 2022
Time period of search	February 15, 2017† - September 15, 2022
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product Name: Arnuity Ellipta NDA #: 205625
MedDRA search terms (Version 25.0)	All PT terms

* See Appendix A for a description of the FAERS database.
† The FAERS search period for the most recently completed DPV pediatric postmarketing pharmacovigilance review for cysteamine bitartrate ended on February 14, 2017.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, NDA=New Drug Application, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from February 15, 2017, through September 15, 2022, with Arnuity Ellipta.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 15, 2017, through September 15, 2022 with Arnuity Ellipta			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	592 (381)	283 (74)	6 (5)
Pediatrics (0 - <17 years)	16 (16)	1 (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, or other serious important medical events.

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

Our FAERS search retrieved one U.S. serious pediatric report from February 15, 2017, through September 15, 2022. We reviewed all U.S. FAERS pediatric reports with a serious outcome; we did not exclude any reports.

Appendix B contains a line listing of the pediatric case.

Reference ID: 5066063

3.1.3 Summary of Fatal) Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases with Arnuity Ellipta.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=1)

We identified one serious FAERS case with Arnuity Ellipta in the U.S. pediatric population reporting a non-fatal outcome. The case is summarized below.

FAERS #13693964 involves a 12-year-old male on Arnuity Ellipta for asthma for less than 6 months. At an unknown time while on Arnuity Ellipta, the patient experienced "strong anxiety and tics and outbursts similar to Tourette's." Once Arnuity Ellipta was stopped, the patient's symptoms improved.

Reviewer's comment: The case provides no details about patient's dose of Arnuity Ellipta and there are missing clinical details regarding the patient's tics and medical history. Additionally, there is no information in the narrative that allows us to rule out provisional tic disorder[4] as the cause of the adverse event A search of the FAERS database was performed on September 19, 2022, for reports with the MedDRA High Level Term Tic Disorder with Arnuity Ellipta in patients of all ages. Additionally, a search of the medical literature was performed for Arnuity Ellipta and tics. The FAERS and literature searches identified no additional cases describing tics with Arnuity Ellipta. We do not have sufficient evidence to support a signal of tics with Arnuity Ellipta at this time.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Arnuity Ellipta in the pediatric population (ages 0 – 16 years) from February 15, 2017, through September 15, 2022. We identified a singular case reporting an unlabeled event of tics. The case lacked clinical information and additional evaluation of the FAERS database and medical literature did not identify sufficient evidence to support a signal of tics with Arnuity Ellipta at this time. We identified no new safety signals and no deaths directly associated with Arnuity Ellipta.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Arnuity Ellipta at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of Arnuity Ellipta.

Reference ID: 5066063

7 REFERENCES

1. Hull K. Medical Officer Review of Arnuity Ellipta (fluticasone furoate) inhalation powder. March 2018. https://www.fda.gov/media/115953/download.
2. Kalra D, Pham T, Harinstein L, Gill R, Muñoz M, Chai G. FDA Office of Surveillance and Epidemiology - Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review-Arnuity Ellipta (fluticasone furoate). 2017. https://www.fda.gov/media/106973/download.
3. Arnuity Ellipta (fluticasone furoate inhalation powder), for oral inhalation use [Prescribing Information]. Research Triangle Park, NC: GlaxoSmithKline; January 2019.
4. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013.

8 APPENDICES

8.1 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 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 (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.

Reference ID: 5066063

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	06/26/2017	13693964	1	N/A	Direct	12	Male	USA	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: OT=other medically significant, USA=United States of America

Reference ID: 5066063

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/

OMAYMA A KISHK
10/25/2022 08:59:47 AM

IVONE E KIM
10/25/2022 09:21:03 AM

CARMEN CHENG
10/25/2022 09:24:11 AM

MONICA MUNOZ
10/25/2022 09:27:53 AM