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 and Drug Utilization Review

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Product Name:	Arnuity Ellipta (fluticasone furoate)
Pediatric Labeling Approval Date:	August 20, 2014
Application Type/Number:	NDA 205625
Applicant/Sponsor:	GlaxoSmithKline
OSE RCM #:	2016-2807

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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 and drug utilization data for Arnuity Ellipta (fluticasone furoate inhalation powder) in pediatric patients.

Arnuity Ellipta was first approved on August 20, 2014, and is indicated for once-daily maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. The Food and Drug Administration Adverse Event Reporting System (FAERS) database was searched for all reports of adverse events received from August 20, 2014, (U.S. approval date) to February 14, 2017 with Arnuity Ellipta. The Division of Pharmacovigilance (DPV) focused on the serious pediatric reports for Arnuity Ellipta.

Drug utilization patterns were assessed to capture pediatric use of Arnuity Ellipta and to provide context for the adverse event reports submitted to the FAERS database. The outpatient retail utilization data showed that pediatric patients 0-16 years of age accounted for 13% (approximately 13,000 patients) of the total patients who were dispensed Arnuity Ellipta prescriptions from August 2014 through February 2017, cumulative. The majority of Arnuity Ellipta pediatric use was among patients 12-16 years of age (73% of pediatric patients). Patients 0-11 years of age accounted for 28% of pediatric patients who were dispensed Arnuity Ellipta prescriptions.

The review of the serious FAERS pediatric cases resulted in the identification of two non-fatal cases with a serious outcome. Of the two cases, one reported vomiting and one reported fatigue. Vomiting and fatigue are labeled as symptoms of adrenal insufficiency in Warnings and Precautions Section 5.4—Transferring Patients from Systemic Corticosteroid Therapy of the Arnuity Ellipta product label. Vomiting and fatigue are not labeled independent of Section 5.4 in the Arnuity Ellipta product label. Of the two cases, one reported vomiting from foreign body aspiration after inhaling Arnuity Ellipta; therefore we are unable to attribute the event to a pharmacologic effect of the medication. The remaining case described a patient who experienced fatigue temporally related to the initiation of Arnuity Ellipta; however, the patient was prescribed Arnuity Ellipta because of lowered lung function from a recent cold and reaction to ragweed, which may be an alternative cause of the fatigue. Given the small number of reports and the number of pediatric patients who received prescriptions for Arnuity Ellipta, these reports do not suggest new safety signals that warrant a labeling update at this time. DPV plans to continue postmarketing surveillance of these events.

1 INTRODUCTION

This review evaluates postmarketing adverse event reports with a serious outcome and drug utilization data for Arnuity Ellipta (fluticasone furoate inhalation powder) in pediatric patients. The approval of Arnuity Ellipta for maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older on August 20, 2014 triggered this review.

1.1 PEDIATRIC REGULATORY HISTORY

Arnuity Ellipta (fluticasone furoate inhalation) 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. For the purpose of this review, we will refer to "fluticasone furoate inhalation powder" as Arnuity Ellipta. Of note, other fluticasone furoate containing products (i.e., nasal spray, inhalation combination product) are not included in this review.

The following regulatory history was reproduced from Dr. Karimi-Shah's (medical officer team leader in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)) cross-discipline team leader review of Arnuity Ellipta.[1]

> Arnuity Ellipta triggered Pediatric Research Equity Act (PREA) and the subsequent need for a development plan in pediatric patients < 12 years of age. The initial pediatric plan was submitted on July 26, 2013, in advance of the New Drug Application (NDA) submission, in which the Applicant requested that a deferral be granted for pediatric patients 5-11 years of age and a waiver be granted for patients <5 years of age. The pediatric plan was presented to the Pediatric Review Committee (PeRC) on September 25, 2013. It was found to be acceptable, with a request to include a hypothalamic-pituitary-adrenal axis study. The Applicant included a revised pediatric study plan with the NDA submission. The second submission was reviewed by PeRC on February 12, 2014, and found to be acceptable."

1.2 SUMMARY OF RELEVANT PREVIOUS POSTMARKETING SAFETY REVIEWS

A Food and Drug Administration Amendments Act (FDAAA) Section 915 Non-New Molecular Entity (non-NME) Postmarket Safety Summary Analysis for Arnuity Ellipta was completed on August 12, 2016.[2] The Division of Pharmacovigilance (DPV) searched the FDA Adverse Event Reporting System (FAERS) database for all serious and non-serious adverse events reported with Arnuity Ellipta from August 20, 2014, (U.S. approval date) to February 29, 2016. The FAERS search yielded 30 reports. Review of all 30 FAERS reports with serious and non-serious outcomes revealed no new potential safety issues requiring regulatory action.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES FOR ARNUITY ELLIPTA[3]

The Arnuity Ellipta product labeling dated November 2014 contains the following safety highlights:

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

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

----------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. 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, discontinue Arnuity Ellipta slowly. (5.5)
- Paradoxical bronchospasm: Discontinue Arnuity Ellipta and institute alternative therapy if paradoxical bronchospasm occurs. (5.7)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.9)
- Monitor growth of adolescent patients. (5.10)
- Close monitoring for glaucoma and cataracts is warranted. (5.11)

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

Most common adverse reactions (reported in greater than or equal to 5% of subjects) are:

- Upper respiratory tract infection, nasopharyngitis, headache, and bronchitis. (6.1)

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Data Sources Used

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions and limitations).

The QuintilesIMS, National Sales Perspectives™ database was used to determine the settings of distribution for Arnuity Ellipta based on the volume of packages sold from the manufacturer to the various settings of care.

The QuintilesIMS, Total Patient Tracker (TPT) database was used to provide national estimates of unique patients who received dispensed prescriptions for Arnuity Ellipta, stratified by patient age (0-11, 12-16, and 17+ years), from August 2014 through February 2017, cumulative.

2.2 RESULTS

2.2.1 Determining Settings of Care

Based on the QuintilesIMS, National Sales Perspectives™ database, approximately 85%, 11%, and 4% of Arnuity Ellipta packages were distributed to outpatient retail pharmacies[4], non-retail settings[5], and mail-order/specialty settings, respectively, from August 2014 through February 2017, cumulative.[6] As a result, we examined Arnuity Ellipta utilization patterns in the outpatient

retail pharmacy setting. Data from non-retail and mail-order/specialty settings were not included in the analysis.

2.2.2 Number of Patients

Table 2.2.2. National estimates of unique patients*, stratified by patient age, who received dispensed prescriptions for Arnuity Ellipta from U.S. outpatient retail pharmacies, cumulative August 2014 through February 2017**

	Cumulative 8/2014-2/2017	
	Patients (N)	%
Arnuity Ellipta	**98,635**	***100.0%***
0 - 16 years	12,729	*12.9%*
0 - 11 years	3,614	*28.4%*
12 - 16 years	9,269	*72.8%*
17+ years	85,298	*86.5%*
Unknown Age	1,155	*1.2%*

Source: QuintilesIMS, Total Patient Tracker™. August 2014 through February 2017. Data extracted March 2017. File: TPT 2016-2807 arnuity ellipta BPCA age 3-30-2017.xls

*Patient subtotals may not sum exactly because patients aged over the examined time. For this reason, summing patients across age groups is not advisable and will result in overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age groups.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

DPV searched the FAERS database with the strategy described in Table 3.1.1. The FAERS search strategy used *Product Name* Arnuity Ellipta and *NDA* 205625, which did not retrieve any reports with other fluticasone furoate containing products (i.e., nasal spray, inhalation combination product). See Appendix B for a description of the FAERS database.

Table 3.1.1 FAERS Search Strategy

Date of Search	March 20, 2017
Time Period of Search	August 20, 2014* - February 14, 2017
Search Type	Quick Query
Product Name(s)	Product Name: Arnuity Ellipta NDA: 205625
Search Parameters	All ages, all outcomes, worldwide

* U.S. approval date and approval date of pediatric labeling

3.2 RESULTS

3.2.1 Total number of FAERS reports by Age

Table 3.2.1 Total adult and pediatric FAERS reports from August 20, 2014 through February 14, 2017 with Arnuity Ellipta (fluticasone furoate inhalation)*

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	72 (67)	16 (11)	1(0)
Pediatrics (0 - <17 years)	7 (7)	**2‡ (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.

‡ The FAERS search strategy used *Product Name* Arnuity Ellipta and *NDA* 205625, which did not retrieve any reports with other fluticasone furoate containing products (nasal spray, inhalation combination product).

3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified two pediatric cases with a non-fatal serious outcome (See Table 3.2.1), which are summarized in Section 3.4.

Appendix C lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

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

There were no fatal pediatric adverse events cases with Arnuity Ellipta from August 20, 2014, through February 14, 2017.

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

We reviewed two pediatric cases that described non-fatal serious adverse events. The cases are briefly described below.

Vomiting (n=1)

Case #12698850, outcome- other serious important medical event, U.S., 2016: A father reported that his 15-year-old male son vomited after inhaling Arnuity Ellipta inhalation powder, 1 puff once daily, for asthma. The patient's past medical history included migraine headache. The patient noted that a quarter inch, white, worm-like object was inhaled into the mouth. After spitting out the object, it made him vomit. Concomitant products included unspecified inhalers and migraine medications. A preliminary investigation via Quality Assurance stated there was no evidence to substantiate the "worm-like object" originated from the Ware[a] site. Arnuity Ellipta was continued with no change. On an unknown date, the outcome of the foreign body aspiration and product complaint were unknown and the outcome of the vomiting was resolving.

[a] Site of manufacturing of Arnuity Ellipta

Reviewer comment: Vomiting is labeled as a symptom of adrenal insufficiency in Warnings and Precautions Section 5.4—Transferring Patients from Systemic Corticosteroid Therapy of the Arnuity Ellipta product label. Vomiting is not labeled independent of Section 5.4 in the Arnuity Ellipta product label. The patient experienced vomiting from foreign body aspiration after inhaling Arnuity Ellipta, therefore we are unable to attribute the event to a pharmacologic effect of the medication. We recommend continued pharmacovigilance of this adverse event.

Fatigue (n=1)

Case # 12742133, outcome- other serious important medical event, U.S., 2016: A mother reported that her 12-year-old male son has become increasingly tired over the past 5 days after starting Arnuity Ellipta inhaler. The mom stated, "he could not go to school, barely standing up. Noticed it started after starting Arnuity." The patient states the tiredness is getting increasingly worse. The patient has seasonal allergies to mold, grasses, weeds, dust mite, and cats. The patient had, "been doing immunotherapy for the past year. Was given the inhaler to take for 4 weeks by his allergist following lowered lung function (82) likely to a combination of recent cold and a reaction to ragweed." Arnuity Ellipta was discontinued. The outcome of fatigue was not reported.

Reviewer comment: Fatigue is labeled as a symptom of adrenal insufficiency in Warnings and Precautions Section 5.4—Transferring Patients from Systemic Corticosteroid Therapy of the Arnuity Ellipta product label. Fatigue is not labeled independent of Section 5.4 in the Arnuity Ellipta product label. The pediatric patient experienced fatigue temporally related to the initiation of Arnuity Ellipta. However, the patient was prescribed Arnuity Ellipta because of lowered lung function from a recent cold and reaction to ragweed, which may be an alternative cause of the fatigue. The response to dechallenge was not reported, but would have been useful in assessing causality.

Because of the temporal relationship between the onset of fatigue and initiation of Arnuity Ellipta in the single pediatric case, we performed an additional FAERS search in the adult population to identify any additional cases of fatigue with Arnuity Ellipta. We identified one non-serious case in a 60-year-old male; however, the case contained insufficient information to properly assess causality (see Appendix D for FAERS search strategy and results). Therefore, we recommend continued pharmacovigilance of this adverse event.

4 DISCUSSION

The outpatient retail utilization data showed that pediatric patients 0-16 years of age accounted for 13% (approximately13,000 patients) of the total patients who were dispensed Arnuity Ellipta prescriptions from August 2014 through February 2017, cumulative. Although the data showed Arnuity Ellipta use in patients under 12 years of age, these use cannot be validated due to the lack of access to patient medical records. Furthermore, our analyses only focused on the outpatient retail setting and might not apply to other settings of care such as inpatient setting and clinics where Arnuity Ellipta may be used.

We evaluated all FAERS reports of serious adverse events in the pediatric population for Arnuity Ellipta from the initial FDA approval and pediatric labeling date of Arnuity Ellipta on August 20,

2014, to February 14, 2017. The review of the FAERS pediatric cases resulted in the identification of two non-fatal cases with a serious outcome. Of the two cases, one reported vomiting and one reported fatigue. Vomiting and fatigue are labeled as symptoms of adrenal insufficiency in Warnings and Precautions Section 5.4—Transferring Patients from Systemic Corticosteroid Therapy of the Arnuity Ellipta product label. Vomiting and fatigue are not labeled independent of Section 5.4 in the Arnuity Ellipta product label. Of the two cases, one reported vomiting from foreign body aspiration after inhaling Arnuity Ellipta; therefore, we are unable to attribute the event to a pharmacologic effect of the medication. The remaining case described a patient who experienced fatigue temporally related to the initiation of Arnuity Ellipta; however, the patient was prescribed Arnuity Ellipta because of lowered lung function from a recent cold and reaction to ragweed, which may be an alternative cause of the fatigue. Given the small number of reports and the number of pediatric patients who received prescriptions for Arnuity Ellipta, these reports do not suggest new safety signals that warrant a labeling update at this time. DPV plans to continue postmarketing surveillance of these events.

5 CONCLUSION

Overall, there were no clear patterns of reported adverse events in the cases to suggest a new safety signal associated with Arnuity Ellipta in pediatric patients. We did not identify any new safety concerns that warrant a labeling update at this time.

6 RECOMMENDATIONS

DPV plans to continue postmarketing surveillance of all adverse events with the use of Arnuity Ellipta in the pediatric patients.

7 REFERENCES

[1] Karimi-Shah Banu, MD. Arnuity Ellipta. Cross-Discipline Team Leader Review. October 22, 2013.
[2] Kalra, Dipti, RPh, Chaudhry, Sofia, MD. 915 Non-New Molecular Entity Postmarket Safety Summary Analysis for Arnuity Ellipta. August 12, 2016.
[3] Arnuity Ellipta [package insert]. Research Triangle Park, NC: GlaxoSmithKline LLC; 2014 (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=50f193ee-1691-486d-9370-a664df63695c Accessed March 20, 2017).
4. Retail settings include chain drug stores, independent drug stores, mass merchandisers, and food stores.
5. Non-retail settings include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.
6. QuintilesIMS, National Sales Perspectives™. August 2014 through February 2017. Data extracted March 2017. File: NSP 2016-2807 arnuity ellipta BPCA channel 3-30-2017.xlsx

8 APPENDICES

8.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS, National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

8.2 APPENDIX B. 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.

8.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=2)

FAERS Case Number	Version Number	Manufacturer Control Number

FAERS Case Number	Version Number	Manufacturer Control Number
12698850	2	US-GLAXOSMITHKLINE-US2016118853
12742133	1	

8.4 APPENDIX D. ADDITIONAL FAERS SEARCH STRATEGY

Table 8.4.1 FAERS Search Strategy	
Date of Search	March 28, 2017
Time Period of Search	August 20, 2014* - February 14, 2017
Search Type	Quick Query
Product Name(s)	Product Name: Arnuity Ellipta NDA: 205625
MedDRA Search Terms (Version 19.1)	PT *Fatigue*
Search Parameters	Age ≥ 17 years

* U.S. approval date and approval date of pediatric labeling

Case #12836347, non-serious, U.S., 2016: A consumer reported that a 60-year-old male patient developed asthenia and fatigue on the day of initiation of Arnuity Ellipta 200 mcg inhaled daily. On an unknown date, the Arnuity Ellipta was decreased to the 100 mcg dose. The patient planned to follow-up with his physician on an unknown date. The asthenia and fatigue were reported as not resolved.

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