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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:	November 8, 2022
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Product Name:	Breo Ellipta (fluticasone furoate/vilanterol trifenatate)
Pediatric Labeling Approval Date:	April 30, 2015
Application Type/Number:	NDA 204275
Applicant:	GlaxoSmithKline
TTT Record ID:	2022-2093

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Breo Ellipta (fluticasone furoate/vilanterol trifenatate) in pediatric patients through age 17 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 fluticasone furoate/vilanterol trifenatate in pediatric patients.

Breo Ellipta is a combination of fluticasone furoate, an inhaled corticosteroid, and vilanterol, a long-acting beta$_2$-adrenergic agonist approved by the FDA on May 10, 2013. Fluticasone furoate/vilanterol trifenatate is currently indicated for 1) long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD) and 2) once-daily treatment of asthma in patients aged 18 years and older. On April 30, 2015, the fluticasone furoate/vilanterol trifenatate product labeling was updated to include the results of the pediatric studies that failed to demonstrate safety and efficacy in pediatric patients aged 17 years and younger. Fluticasone furoate/vilanterol trifenatate is not indicated for use in children and adolescents <18 years of age.

DPV reviewed all U.S. serious FAERS reports for fluticasone furoate/vilanterol trifenatate in the pediatric population (ages 0 <18 years) from May 10, 2013, through September 29, 2022. The FAERS search identified eight U.S. serious reports. After hands-on review, all reports were excluded from further discussion. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to fluticasone furoate/vilanterol trifenatate.

DPV will continue to monitor all adverse events associated with the use of fluticasone furoate/vilanterol trifenatate.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Breo Ellipta (fluticasone furoate/vilanterol trifenatate) in pediatric patients through age 17 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 fluticasone furoate/vilanterol trifenatate in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Breo Ellipta is a combination of fluticase furoate, an inhaled corticosteroid, and vilanterol, a long-acting beta$_2$-adrenergic agonist (LABA) approved by the FDA on May 10, 2013. Fluticasone furoate/vilanterol trifenatate is currently indicated for 1) long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD) and 2) once-daily treatment of asthma in patients aged 18 years and older. On April 30, 2015, the FDA approved fluticasone furoate/vilanterol trifenatate for the treatment of asthma in patients aged 18 years and older; the product labeling was updated to include the results of the pediatric studies that failed to demonstrate safety and efficacy in pediatric patients aged 12-17 years. Fluticasone furoate/vilanterol trifenatate is not indicated for use in children and adolescents <18 years of age.[1]

The asthma development program for fluticasone furoate/vilanterol trifenatate was designed to demonstrate the efficacy of fluticasone furoate/vilanterol trifenatate compared to placebo, the contribution of vilanterol to the combination, and the added benefit of the higher dose (200/25) over the lower dose (100/25). Information to support the efficacy and safety of fluticasone furoate/vilanterol trifenatate for the maintenance treatment of asthma is derived primarily from four clinical trials (NCT01165138, NCT01686633, NCT01134042, and NCT01086384).[2-5] One additional long-term, 52-week safety study (NCT01018186), provided additional safety data for fluticasone furoate/vilanterol trifenatate.[6] In the asthma exacerbation trial (NCT01086384), 2,019 subjects received fluticasone furoate/vilanterol trifenatate or fluticasone furoate of variable duration (≥24-78 weeks) in a randomized, double-blind, comparative study. The primary outcome of this trial was the time to first severe asthma exacerbation. Adolescents aged 12 to 17 years comprised of 14% of the study population. In adolescents, there was a numerical trend towards a smaller observed treatment effect in the fluticasone furoate/vilanterol trifenatate treatment group compared to fluticasone furoate alone. Additionally, there was a numerical trend towards increased risk of asthma exacerbation with fluticasone furoate/vilanterol trifenatate compared to fluticasone furoate. Asthma-related hospitalizations among adolescents occurred in four patients in the fluticasone furoate/vilanterol trifenatate treatment group (compared to none in the fluticasone furoate treatment group).[1] The pediatric data from the asthma exacerbation trial are summarized the the product labeling (see Section 1.2 Relevant Labeled Safety Information of this review, below, under Pediatric Use section of labeling).

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling change for fluticasone furoate/vilanterol trifenatate on April 30, 2015. DPV has not previously presented fluticasone furoate/vilanterol trifenatate to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The fluticasone furoate/vilanterol trifenatate labeling contains the following safety information excerpted from the Highlights section of the labeling as well as the Pediatric Use subsection.[7] For further labeling information, please refer to the full prescribing information.

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

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

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

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Do not initiate in acutely deteriorating COPD or asthma. Do not use to treat acute symptoms. (5.2)
- Do not use in combination with an additional medicine containing a LABA because of risk of overdose. (5.3)
- *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)
- Increased risk of pneumonia in patients with COPD. Monitor patients for signs and symptoms of pneumonia. (5.5)
- 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. (5.6)

- Risk of impaired adrenal function when transferring from systemic corticosteroids. Taper patients slowly from systemic corticosteroids if transferring to BREO ELLIPTA. (5.7)
- Hypercorticism and adrenal suppression may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue BREO ELLIPTA slowly. (5.8)
- If paradoxical bronchospasm occurs, discontinue BREO ELLIPTA and institute alternative therapy. (5.10)
- Use with caution in patients with cardiovascular disorders because of beta-adrenergic stimulation. (5.12)
- Assess for decrease in bone mineral density initially and periodically thereafter. (5.13)
- Glaucoma and cataracts may occur with long-term use of ICS. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREO ELLIPTA long term. (5.14)
- Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Increased blood glucose levels have been reported. Also, be alert to hypokalemia. (5.16)

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

- COPD: Most common adverse reactions (incidence ≥3%) are nasopharyngitis, upper respiratory tract infection, headache, oral candidiasis, back pain, pneumonia, bronchitis, sinusitis, cough, oropharyngeal pain, arthralgia, hypertension, influenza, pharyngitis, and pyrexia. (6.1)
- Asthma: Most common adverse reactions (incidence ≥2%) are nasopharyngitis, oral candidiasis, headache, influenza, upper respiratory tract infection, bronchitis, sinusitis, oropharyngeal pain, dysphonia, and cough. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS**----------

- Strong cytochrome P450 3A4 inhibitors (e.g., ketoconazole): Use with caution. May cause systemic corticosteroid and cardiovascular effects. (7.1)
- Monoamine oxidase inhibitors and tricyclic antidepressants: Use with extreme caution. May potentiate effect of vilanterol on vascular system. (7.2)
- Beta-blockers: Use with caution. May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. (7.3)
- Diuretics: Use with caution. Electrocardiographic changes and/or hypokalemia associated with non–potassium-sparing diuretics may worsen with concomitant beta-agonists. (7.4)

8.4 Pediatric Use

BREO ELLIPTA is not indicated for use in children and adolescents. The safety and efficacy in pediatric patients (aged 17 years and younger) have not been established.

In a 24- to 76-week exacerbation trial, subjects received BREO ELLIPTA 100/25 (n = 1,009) or fluticasone furoate 100 mcg (n = 1,010). Subjects had a mean age of 42 years and a history of 1 or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma in the year prior to study entry. *[See Clinical Studies (14.2).]* Adolescents aged 12 to 17 years made up 14% of the study population (n = 281), with a mean exposure of 352 days for subjects in this age group treated with BREO ELLIPTA 100/25 (n = 151) and 355 days for subjects in this age group treated with fluticasone furoate 100 mcg (n = 130). In this age group, 10% of subjects treated with BREO ELLIPTA 100/25 reported an asthma exacerbation compared with 7% for subjects treated with fluticasone furoate 100 mcg. Among the adolescents, asthma-related hospitalizations occurred in 4 subjects (2.6%) treated with BREO ELLIPTA 100/25 compared with 0 subjects treated with fluticasone furoate 100 mcg. There were no asthma-related deaths or asthma-related intubations observed in the adolescent age group.

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 BREO 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 BREO 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 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 (5.17)]*.

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 30, 2022
Time period of search	May 10, 2013† - September 29, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: fluticasone furoate\vilanterol trifenatate
MedDRA search terms (Version 25.0)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. Approval Date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

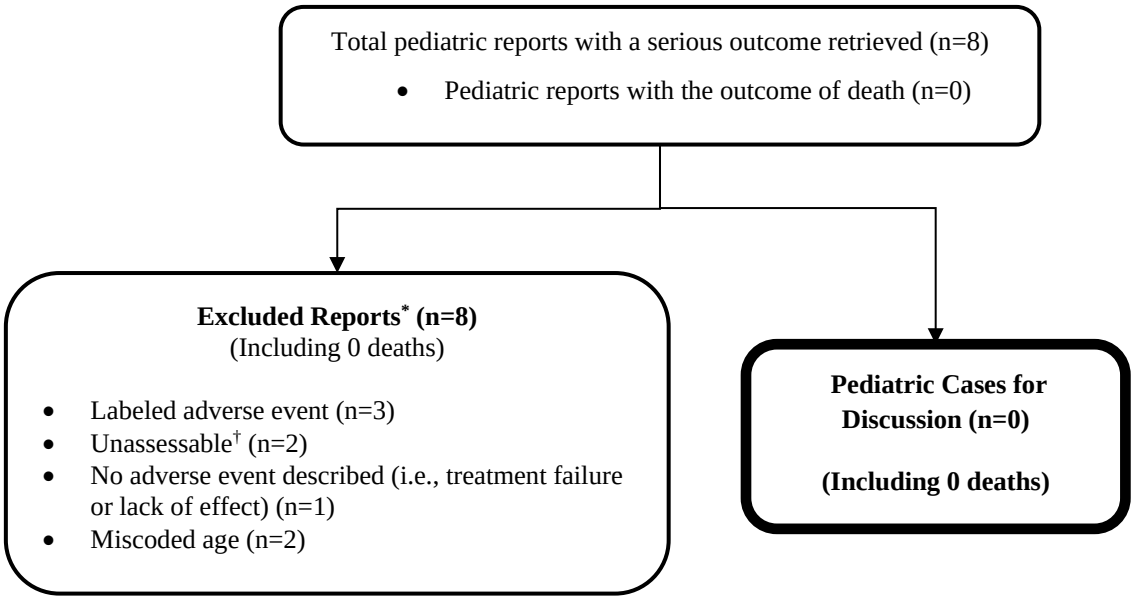
Table 2 presents the number of adult and pediatric FAERS reports from May 10, 2013, through September 29, 2022, with fluticasone furoate/vilanterol trifenatate.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From May 10, 2013, through September 29, 2022, With Fluticasone Furoate/Vilanterol Trifenatate			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	8,561 (5,663)	4,515 (1,646)	278 (146)
Pediatrics (0 - <18 years)	113 (70)	49 (8)	3 (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 eight U.S. serious pediatric reports from May 10, 2013, through September 29, 2022. We excluded all eight reports from the case series for the following reasons: labeled adverse event (n=3), unassessable reports (n=2), miscoded age (n=2), or no adverse event described (n=1). **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious U.S. Pediatric Cases with Fluticasone Furoate/Vilanterol Trifenatate



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above

† Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory or information provided in the report cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for further discussion with fluticasone furoate/vilanterol trifenatate.

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

We did not identify any unlabeled non-fatal adverse event cases associated with fluticasone furoate/vilanterol trifenatate in the pediatric population.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports for fluticasone furoate/vilanterol trifenatate in the pediatric population (ages 0 <18 years) from May 10, 2013, through September 29, 2022. No reports were included in the case series as the reports described adverse events that were already included in the fluticasone furoate/vilanterol trifenatate labeling, were unassessable, had miscoded age, or had no adverse event described. There were no safety signals, no increased

severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to fluticasone furoate/vilanterol trifenatate.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for fluticasone furoate/vilanterol trifenatate at this time.

6 RECOMMENDATION

DPV will continue to monitor all adverse events associated with the use of fluticasone furoate/vilanterol trifenatate.

7 REFERENCES

1. Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee FDA Briefing Document for sNDA 204-275: fluticasone furoate and vilanterol inhalation powder for the maintenance treatment of asthma in patients 12 years of age and older. March 19, 2015, available at https://wayback.archive-it.org/7993/20170405213724/https:/www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM438379.pdf.
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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.

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