

**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 Review

Date: February 22, 2019

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Product Name(s): Symbicort (budesonide/formoterol fumarate dihydrate)

**Pediatric Labeling
Approval Date:** January 27, 2017

Application Type/Number: 021929

Applicant/Sponsor: AstraZeneca

OSE RCM #: 2018-2772

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Symbicort (budesonide/formoterol fumarate dihydrate) in pediatric patients less than 17 years of age. 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 serious unlabeled adverse events associated with Symbicort in pediatric patients.

Symbicort (budesonide/formoterol fumarate dihydrate, NDA 021929) is a combination product containing an inhaled corticosteroid (ICS) and a long-acting beta₂-adrenergic agonist (LABA). Symbicort was initially approved by FDA on July 21, 2006, for the long-term maintenance treatment of asthma in patients 12 years of age and older. On February 27, 2009, Symbicort was approved for the treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. On January 27, 2017, Symbicort's asthma indication was expanded to include patients 6 years of age and older. Symbicort is available as a metered-dose inhaler in two different dosage strengths, 80/4.5 mcg and 160/4.5 mcg, containing doses of 80 or 160 mcg of budesonide and 4.5 mcg of formoterol per inhalation; the choice of inhaler is based on patient age (6 to less than 12 years or 12 years and older) and indication for use (asthma or COPD).

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for Symbicort in the FAERS database from July 21, 2006 (U.S. approval date), to December 9, 2018. We identified one foreign pediatric case of drug reaction with eosinophilia and systemic symptoms (DRESS), however we are unable to exclude the role of another concomitant medication in the development of the event. To further assess the potential association between Symbicort and DRESS, we searched the FAERS database for any additional cases in the adult population. We identified two foreign cases of adult patients who developed DRESS two weeks and an unknown time after receiving Symbicort, but both cases contained possible alternative causes for the event.

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 Symbicort.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Symbicort (budesonide/formoterol fumarate dihydrate) in pediatric patients less than 17 years of age. 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 serious unlabeled adverse events associated with Symbicort in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Symbicort (budesonide/formoterol fumarate dihydrate, NDA 021929) is a combination product containing an inhaled corticosteroid (ICS) and a long-acting beta₂-adrenergic agonist (LABA). Symbicort was initially approved by FDA on July 21, 2006, for the long-term maintenance treatment of asthma in patients 12 years of age and older. On February 27, 2009, Symbicort was approved for the treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. On January 27, 2017, Symbicort's asthma indication was expanded to include patients 6 years of age and older. Symbicort is available as a metered-dose inhaler in two different dosage strengths, 80/4.5 mcg and 160/4.5 mcg, containing doses of 80 or 160 mcg of budesonide and 4.5 mcg of formoterol per inhalation; the choice of inhaler is based on patient age (6 to less than 12 years or 12 years and older) and indication for use (asthma or COPD).

There have been longstanding safety concerns regarding an increase in asthma-related death in adults and an increased risk of asthma-related hospitalization in children exposed to LABAs. In December 2008, an FDA Advisory Committee (AC) discussed the safety of LABAs in patients with asthma, including results of a meta-analysis that suggested an age-related trend of increased asthma-related hospitalizations in pediatric patients. During the AC meeting, the committee stressed the need for more safety data, especially in the pediatric population where the data were very limited.¹ In 2010, FDA required safety trials be conducted in adults and children with the LABA products that were approved for the treatment of asthma to further evaluate the safety concerns of this drug class in the asthmatic population.² In 2017, an FDA review of four large clinical safety trials showed that treating asthma with LABAs in combination with ICS does not result in significantly more serious asthma-related side effects than treatment with ICS alone. Based on the review, the *Boxed Warning* about asthma-related death was removed from the drug labels of medicines that contain both an ICS and LABA, including removal from the Symbicort product label on December 20, 2017.³

1.2 RELEVANT LABELED SAFETY INFORMATION

Select safety highlights that appear in the Symbicort product label dated December 2017 are listed below.⁴

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

- Serious asthma-related events: Long-acting beta₂-adrenergic agonists as monotherapy increase the risk.
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or COPD or to treat acute symptoms.

- Use with additional long-acting beta₂-agonist: Do not use in combination because of risk of overdose.
- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise the patient to rinse his/her mouth with water without swallowing after inhalation to help reduce the risk.
- Pneumonia: Increased risk in patients with COPD. Monitor patients for signs and symptoms of pneumonia and other potential lung infections.
- Immunosuppression: Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or 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 oral steroids. Taper patients slowly from systemic corticosteroids if transferring to SYMBICORT.
- Hypercorticism and adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue SYMBICORT slowly.
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with SYMBICORT.
- Paradoxical bronchospasm: Discontinue SYMBICORT and institute alternative therapy if paradoxical bronchospasm occurs.
- Patients with cardiovascular or central nervous system disorders: Use with caution because of beta-adrenergic stimulation.
- Decreases in bone mineral density: Assess bone mineral density initially and periodically thereafter.
- Effects on growth: Monitor growth of pediatric patients.
- Glaucoma and cataracts: Close monitoring is warranted.
- Metabolic effects: Be alert to eosinophilic conditions, hypokalemia, and hyperglycemia.
- Coexisting conditions: Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis.

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

- Most common adverse reactions (incidence ≥3%) are:
- Asthma: nasopharyngitis, headache, upper respiratory tract infection, pharyngolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis.
- COPD: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, upper respiratory tract infections.

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	December 10, 2018
Time Period of Search	July 21, 2006 [†] - December 9, 2018
Search Type	FBIS Quick Query
Product Terms	Product active ingredient: budesonide/formoterol, budesonide/formoterol fumarate, budesonide/formoterol fumarate dihydrate NDA: 021929
MedDRA Search Terms (Version 21.1)	All Preferred Terms (PTs)
Search Parameters	All ages, all outcomes, worldwide

Table 1. FAERS Search Strategy*
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* 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

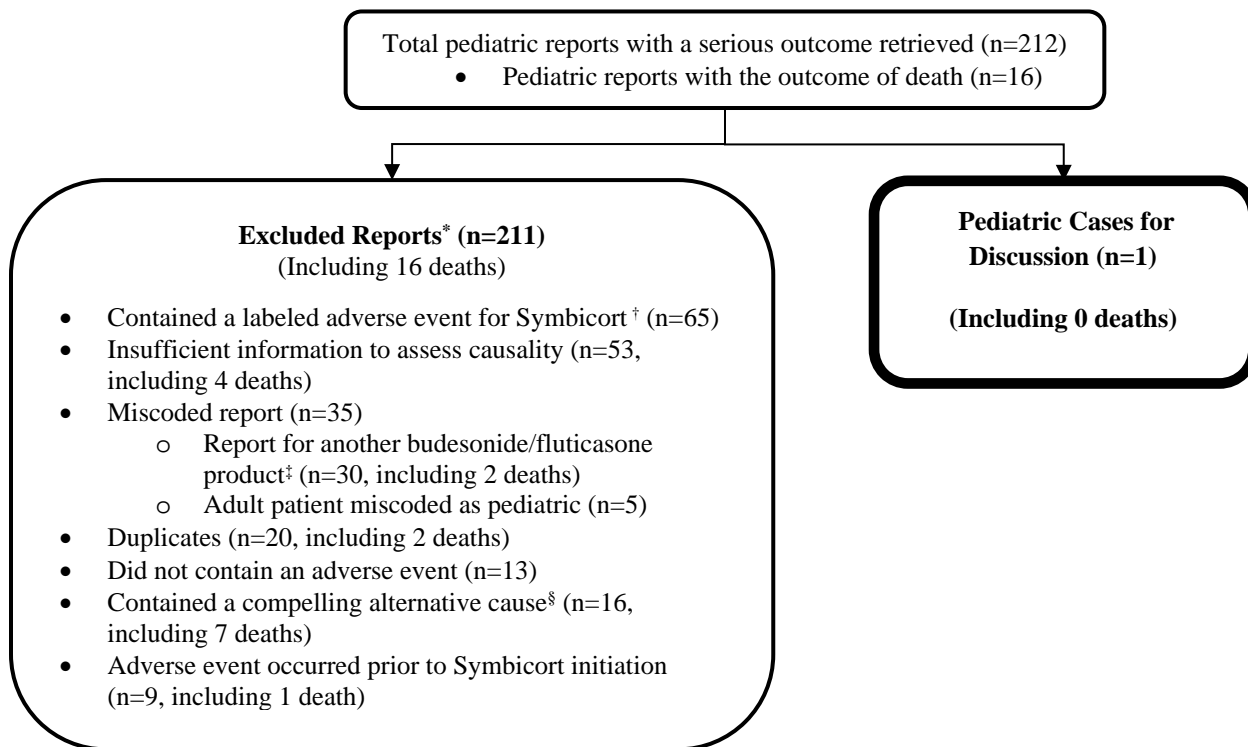
Table 2 presents the number of adult and pediatric FAERS reports from July 21, 2006, to December 9, 2018, with Symbicort.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from July 21, 2006, to December 9, 2018, with Symbicort			
	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 17 years)	16,119 (12,416)	7,944 (4,282)	888 (407)
Pediatrics (0 - <17 years)	406 (251)	212‡ (59)	16 (9)
* 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 Symbicort.			

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

Our FAERS search retrieved 212 serious pediatric reports from July 21, 2006, to December 9, 2018. Figure 1 presents the selection of cases for the pediatric case series.

Figure 1. Selection of Serious Pediatric Cases with Symbicort



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

† The labeled adverse events for Symbicort included: bronchospasm (n=15), tremor (n=8), depression (n=5), rash (n=4), behavioral disturbances (n=4), chest pain (n=3), hypersensitivity (n=3), atrial and ventricular tachyarrhythmias (n=2), candidiasis (n=2), cough (n=2), muscular pain (n=2), vomiting (n=2), dizziness (n=1), drug interaction with itraconazole (n=1), eczema (n=1), growth retardation (n=1), hypercorticism (n=1), influenza (n=1), palpitation (n=1), pneumonia (n=1), pruritus (n=1), pyrexia (n=1), reduction in bone density (n=1), tachycardia (n=1), oral viral infection (n=1).

‡ We reviewed the cases reporting other budesonide/fluticasone products and we did not identify any new potential signals.

§ The adverse events in nine reports were related to the patient's underlying asthma or COPD including six cases of fatal status asthmaticus. Two reports contained adverse events more likely attributable to concomitant medications such as dyskinesia with domperidone (n=1), and thrombocytopenia with omalizumab (n=1). The remaining five reports contained adverse events attributable to another comorbidity or disease: achilles tendonitis secondary to calcaneous bone spur (n=1), haematochezia in a patient with a medical history of bloody stools (n=1), sudden death in sleep in an obese patient whose autopsy revealed an unspecified cardiomyopathy as cause of death (n=1), fever secondary to an acute coxsackie viral infection (n=1), and increased prolactin levels in a patient with pituitary gland microadenoma (n=1).

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not include any fatal pediatric adverse event cases in our case series.

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

We identified one foreign case associated with a serious outcome containing the unlabeled adverse event of drug reaction with eosinophilia and systemic symptoms (DRESS) in a pediatric patient receiving Symbicort.

FAERS Case #10399638, hospitalization, FRA, 2014:

The French Medicine Agency reported that a 10-year-old male patient with no significant medical history received one puff of Symbicort (budesonide, formoterol) inhaled and

oxomemazine 10 ml orally per day for three days for the treatment of cough. Eight days later, the patient developed a fever of greater than 39° Celsius. The next day, the patient experienced pruritic skin eruption on the abdomen that spread to the trunk and the limbs but spared the palms and soles. The next day, the patient was admitted to hospital due to persistent fever and rash and new findings of pharyngitis and adenopathy to cervical, axillary, and inguinal regions. Laboratory evaluation was notable for elevated alanine aminotransferase, hyperbilirubinemia, and white blood cell differential had hypereosinophilia without atypical lymphocytes. The remainder of the evaluation for autoimmune and infectious workup was normal. The patient's pruritis improved and his rash evolved into desquamative lesions. The patient was diagnosed with DRESS with a score of 5 on the RegiSCAR scale.^a

Reviewer Comment: *DRESS is an adverse drug reaction notable for cutaneous eruptions and end organ involvement with an associated mortality rate of 10%.⁵ The time to onset and constellation of symptoms described in this case are consistent with DRESS and the RegiSCAR score of 4-5 indicates a probable case of DRESS.⁶ However, it is difficult to attribute causality to the Symbicort in this case as the patient received concomitant oxomemazine, a phenothiazine-derivative, sedating antihistamine available in France.⁷*

To further assess the potential association between Symbicort and DRESS, we searched the FAERS database for additional cases in the adult population. We identified two foreign cases of adult patients who developed DRESS after receiving Symbicort. Time to onset was 2 weeks in one case and unspecified in the other case. The cases had RegiSCAR scores of 6, indicating a definitive case of DRESS. However, both cases described concomitant medications labeled for severe cutaneous adverse reactions; one patient took perindopril erbumine which is labeled for bullous pemphigoid, exfoliative dermatitis, and pemphigus and the other patient took pemetrexed which is labeled for bullous and exfoliative skin toxicity.^{8,9} It is not possible to determine the extent to which these concomitant medications contributed to the clinical findings that led to the DRESS diagnosis. DPV will continue routine pharmacovigilance because of the paucity of well-documented cases of DRESS associated with Symbicort use.

4 DISCUSSION

We evaluated all pediatric postmarketing adverse event reports with a serious outcome for Symbicort in the FAERS database from July 21, 2006 (U.S. approval date), to December 9, 2018. We did not identify any fatal pediatric adverse event cases. We identified one pediatric case of DRESS, however we are unable to exclude the role of another concomitant medication in the development of the event. Therefore, no new safety signals were identified and there was no increase in the severity or frequency of labeled adverse events.

5 CONCLUSION

DPV-I did not identify any pediatric safety concerns for Symbicort at this time.

^a RegiSCAR, a multinational European project dedicated to studying severe cutaneous adverse reactions (SCARs), maintains a registry of SCAR cases (SJS, TEN, AGEP, and DRESS). They also collect biological samples to study the pathomechanisms and genetic factors associated with SCAR.

6 RECOMMENDATION

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

7 REFERENCES

1. Seymour, Sally. Summary Review for Regulatory Action. December 20, 2017.
2. FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), February 18, 2010.
3. FDA Drug Safety Communication: FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). December 20, 2017.
4. Symbicort [package insert]. Wilmington, DE; Revised December 2017.
5. Husain Z et al. DRESS syndrome. *J Am Acad Dermatol.* 2013;68:693.e1-14.
6. Cacoub P, Musette P, Descamps V, et. al. The DRESS Syndrome: A Literature Review. *The American Journal of Medicine.* Volume 124, No 7, July 2011.
7. Oxomemazine: Adverse effects. (2019). In Micromedex. (Columbia Basin College Library ed.). [Electronic version]. Greenwood Village, CO: Truven Health Analytics. Retrieved January 29, 2019.
8. Perindopril erbumine [package insert]. East Windsor, NJ; Revised September 2018.
9. Pemetrexed [package insert]. Wilmington, DE; Revised December 2017.

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.

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	8/21/2014	10399638	1	FR-ASTRAZENECA-2014SE59599	Expedited (15-Day)	10	Male	FRA	HO
<p>*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, or a congenital anomaly/birth defect, and 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: HO=Hospitalization</p>									

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/s/

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