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 24, 2023
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Product Name:	Dulera (formoterol fumarate\mometasone furoate) inhalation aerosol
Pediatric Labeling Approval Date:	August 12, 2019
Application Type/Number:	NDA 22518
Applicant:	Organon, LLC
TTT Record ID:	2023-5812

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dulera (formoterol fumarate\mometasone furoate dihydrate) inhalation aerosol 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 unlabeled adverse events associated with Dulera in pediatric patients.

Dulera (formoterol fumarate\mometasone furoate dihydrate) is a combination product containing a long-acting $beta_2$ agonist and a corticosteroid. Dulera was initially approved in the United States on June 22, 2010. Dulera is currently indicated for the treatment of asthma in patients 5 years of age and older.

This pediatric postmarketing safety review was prompted by pediatric labeling on August 12, 2019, that extended the indication to include use in pediatric patients aged 5 – 11 years. The safety and effectiveness of Dulera have not been established in patients younger than 5 years old.

On March 16, 2012, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for Dulera in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Dulera.

DPV reviewed all FAERS reports with Dulera in pediatric patients less than 18 years of age from January 1, 2012 – July 24, 2023, and identified 30 reports. However, all reports were excluded from further discussion.

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

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dulera (formoterol fumarate\mometasone furoate dihydrate) inhalation aerosol 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 unlabeled adverse events associated with Dulera in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Dulera (formoterol fumarate\mometasone furoate dihydrate) is a combination product containing a long-acting beta$_2$-adrenergic agonist and a corticosteroid. Dulera was initially approved in the United States on June 22, 2010. Dulera is currently indicated for the treatment of asthma in patients 5 years of age and older.[1]

This pediatric postmarketing safety review was prompted by pediatric labeling on August 12, 2019, that extended the indication to include use in pediatric patients aged 5-11 years. The safety and effectiveness of Dulera have not been established in patients younger than 5 years old.[1]

On March 16, 2012, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for Dulera in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Dulera.[2]

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Dulera labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Dulera 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)
- Hypersensitivity to any of the ingredients of DULERA. (4.2)

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

- LABA monotherapy increases the risk of serious asthma-related events. (5.1)
- Deterioration of disease and acute episodes: Do not initiate in acutely deteriorating asthma or to treat acute symptoms. (5.2)
- Use with additional long-acting beta2-agonist: Do not use in combination because of risk of overdose. (5.3)
- Localized infections: Candida albicans infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. After dosing, advise patients to rinse their mouth with water and spit out contents without swallowing. (5.4)
- Immunosuppression: Potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients. Use with caution in patients with these infections because of the potential for worsening of these infections. (5.5)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to DULERA. (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 DULERA slowly. (5.7)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with DULERA. (5.8)
- Paradoxical bronchospasm: Discontinue DULERA and institute alternative therapy if paradoxical bronchospasm occurs. (5.9)
- Patients with cardiovascular disorders: Use with caution 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)
- Effects on growth: Monitor growth of pediatric patients. (5.13)
- Glaucoma and cataracts: Consider referral to an ophthalmologist in patients who develop ocular symptoms or use DULERA long term. (5.14)
- Coexisting conditions: Use with caution in patients with aneurysm, pheochromocytoma, convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. (5.15)
- Hypokalemia and hyperglycemia: Be alert to hypokalemia and hyperglycemia. (5.16)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (reported in ≥3% in any treatment arm and greater than placebo) included:
- Nasopharyngitis, sinusitis and headache. (6.1)

8.4 Pediatric Use
The safety and effectiveness of DULERA have been established in patients 12 years of age and older in 3 clinical trials up to 52 weeks in duration. In the 3 clinical trials, 101 patients 12 to 17 years of age were treated with DULERA. Patients in this age-group demonstrated efficacy results similar to those observed in patients 18 years of age and older. There were no obvious differences in the type or frequency of adverse reactions reported in this age group compared to patients 18 years of age and older. Similar efficacy and safety results were observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial.

The safety and effectiveness of DULERA 50 mcg/5 mcg, two inhalations twice daily, have been established in patients with asthma aged 5 to less than 12 years in clinical trials up to 24 weeks of treatment duration. Patients in this age group demonstrated efficacy and safety results similar to those observed in patients aged 12 years and older who were treated with DULERA [see Adverse Reactions (6.1) and Clinical Studies (14.1)].

The safety and effectiveness of DULERA have not been established in children younger than 5 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients 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 DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose [see Dosage and Administration (2.2)].

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	July 25, 2023
Time period of search	January 1, 2012† - July 24, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Product terms	Product Active Ingredient: Formoterol fumarate\mometasone furoate
MedDRA search terms (Version 26.0)	All Preferred Terms

* See Appendix A for a description of the FAERS database.
† Data lock date from OSE's previous pediatric postmarketing pharmacovigilance review for formoterol fumarate\mometasone furoate.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities

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 January 1, 2012 – July 24, 2023, with Dulera.

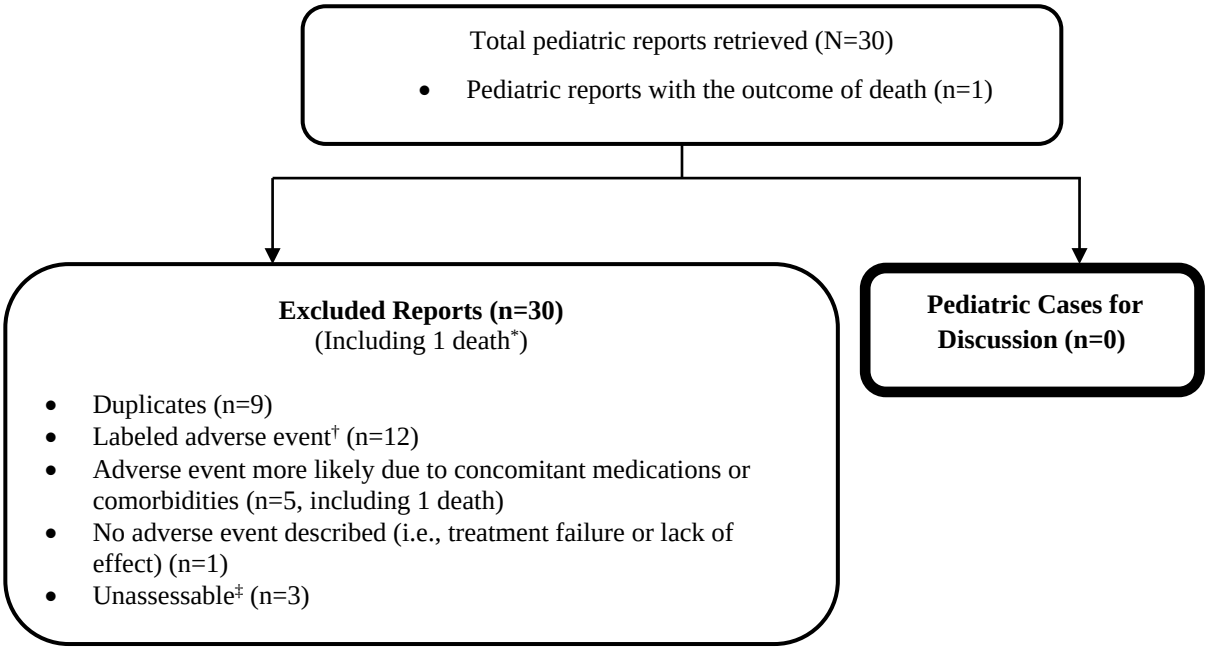
Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 1, 2012 – July 24, 2023, With Dulera			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1443 (9)	1441 (8)	17 (3)
Pediatrics (0 - < 18 years)	30 (2)	29 (1)	1 (0)

* 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 Pediatric Cases in FAERS

Our FAERS search retrieved 30 pediatric reports from January 1, 2012 – July 24, 2023, with Dulera. We reviewed all FAERS pediatric reports. We excluded all 30 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 Pediatric Cases With Dulera



* One excluded FAERS report described a fatal outcome. The death occurred as a result of a severe asthma exacerbation during treatment with another medication. The death was not attributed to Dulera.
† Labeled adverse event does not represent increased severity or frequency.
‡ Unassessable: The 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), 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 discussion.

3.1.4 Summary of Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV reviewed all FAERS reports with Dulera in pediatric patients less than 18 years of age from January 1, 2012 – July 24, 2023, and identified 30 reports; however, all reports were excluded from further discussion.

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

5 CONCLUSION

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

6 REFERENCES

1. Dulera (mometasone furoate and formoterol fumarate dihydrate) inhalation aerosol, for oral inhalation use. [Prescribing information]. Whitehouse Station, NJ:Merck & Co., Inc.; August, 2019.

2. Kalra, D. Pediatric Postmarket Adverse Event Review. March 16, 2012.

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.

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