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:	Asmanex HFA (mometasone furoate)
Pediatric Labeling Approval Date:	August 12, 2019
Application Type/Number:	NDA 205641
Applicant:	Merck & Co., Inc.
TTT Record ID:	2023-5816

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Asmanex HFA (mometasone furoate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Asmanex HFA in pediatric patients.

Asmanex HFA (mometasone furoate) is an inhaled corticosteroid initially approved in the U.S. on April 25, 2014. Asmanex HFA is currently indicated for maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. Asmanex HFA metered inhalers are available in three strengths: 50 mcg/inhalation, 100 mcg/inhalation, and 200 mcg/inhalation.

This pediatric postmarketing safety review was prompted by pediatric labeling on August 12, 2019, which expanded Asmanex HFA's indication for use in patients aged 5 to 11 years old. The safety and effectiveness of Asmanex HFA have not been established in children younger than 5 years.

On May 16, 2017, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for mometasone furoate in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with mometasone furoate.

DPV reviewed all serious FAERS reports with Asmanex HFA in pediatric patients less than 18 years of age from January 1, 2017 – July 24, 2023, and identified six serious pediatric 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 Asmanex HFA in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Asmanex HFA (mometasone furoate) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Asmanex HFA in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Asmanex HFA (mometasone furoate) is an inhaled corticosteroid initially approved in the U.S. on April 25, 2014. Asmanex HFA is currently indicated for maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older.[1] Asmanex HFA metered inhalers are available in three strengths: 50 mcg/inhalation, 100 mcg/inhalation, and 200 mcg/inhalation. Of note, another mometasone furoate inhalation product, Asmanex Twisthaler (mometasone furoate inhalation powder, NDA 21067), was originally approved by FDA on March 30, 2005, and this product is currently indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older.[2]

This pediatric postmarketing safety review was prompted by the pediatric labeling on August 12, 2019, which expanded Asmanex HFA's indication for use in patients aged 5 to 11 years old. The safety and effectiveness of Asmanex HFA have been established in patients with asthma aged 5 to 11 years old in clinical trials up to 24 weeks of duration. The safety profile and overall effectiveness in this age group were consistent with that of older patients. The safety and effectiveness of Asmanex HFA have not been established in children aged <5 years.[1]

On May 16, 2017, the Office of Surveillance and Epidemiology (OSE) completed a review of postmarketing adverse event reports with a serious outcome for mometasone furoate in pediatric patients. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with mometasone furoate.[3]

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Asmanex HFA labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Asmanex HFA 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 ASMANEX HFA. (4.2)

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

- Deterioration of asthma and acute episodes: ASMANEX HFA should not be used for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.1)
- 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 patients to rinse the mouth following inhalation. (5.2)

- 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. (5.3)
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Wean patients slowly from systemic corticosteroids if transferring to ASMANEX HFA. (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 ASMANEX HFA slowly. (5.5)
- Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with ASMANEX HFA. (5.6)
- Paradoxical bronchospasm: Discontinue ASMANEX HFA and institute alternative therapy if paradoxical bronchospasm occurs. (5.7)
- Hypersensitivity reactions including anaphylaxis: Hypersensitivity reactions, such as urticaria, flushing, allergic dermatitis, bronchospasm, rash, pruritus, angioedema, and anaphylactic reaction may occur. Discontinue ASMANEX HFA if such reactions occur. (5.8)
- Decreases in bone mineral density: Monitor patients with major risk factors for decreased bone mineral content. (5.9)
- Effects on growth: Monitor growth of pediatric patients. (5.10)
- Glaucoma and cataracts: Consider referral to an ophthalmologist in patients who develop ocular symptoms or use ASMANEX HFA long term. (5.11)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (reported in greater than or equal to 3% of patients) included:
- nasopharyngitis, headache, sinusitis, bronchitis, and influenza. (6.1)

8.4 Pediatric Use
The safety and effectiveness of ASMANEX HFA have been established in patients 12 years of age and older in 2 clinical trials of 12 and 26 weeks in duration. In the 2 clinical trials, 32 patients 12 to 17 years of age were treated with ASMANEX HFA. No overall differences in effectiveness were observed between patients in this age group compared to those observed in patients 18 years of age and older. There were no obvious differences in the type or frequency of adverse drug reactions reported in this age group compared to patients 18 years of age and older.

The safety and effectiveness of ASMANEX HFA 50 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. The safety profile and overall effectiveness in this age group were consistent with that
observed in patients aged 12 years and older who also received ASMANEX HFA [see Adverse Reactions
(6.1) and Clinical Studies (14.1)].

The safety and effectiveness of ASMANEX HFA 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 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 ASMANEX HFA, 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 ASMANEX HFA, 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, 2017† - July 24, 2023
Search type	Drug Safety Analytics Dashboard (DSAD) Quick Query
Search terms	Product Name: Asmanex, Asmanex HFA NDA: 205641
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data lock date from the last OSE pediatric postmarketing pharmacovigilance assessment for mometasone furoate. Abbreviations: HFA=hydrofluoroalkane, MedDRA=Medical Dictionary for Regulatory Activities, NDA=New drug application	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

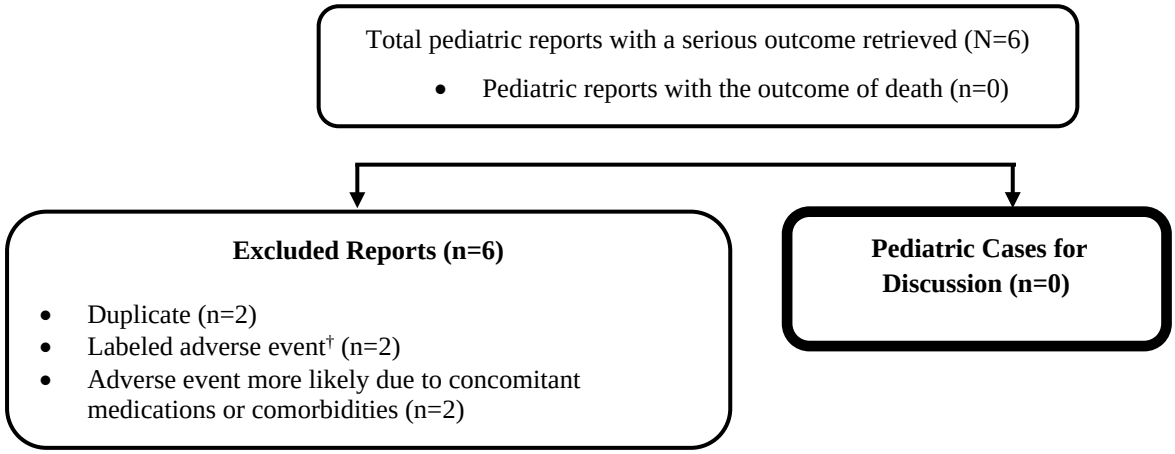
Table 2 presents the number of adult and pediatric FAERS reports from January 1, 2017 – July 24, 2023, with Asmanex HFA.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From January 1, 2017 – July 24, 2023, With Asmanex HFA			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1259 (1228)	117 (89)	2 (2)
Pediatrics (0 - < 18 years)	162 (158)	6 (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, or other serious important medical events.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved six serious pediatric reports from January 1, 2017 – July 24, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded all six 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 Serious Pediatric Cases With Asmanex HFA



* Labeled adverse event does not represent increased severity or frequency.

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 Serious Non-Fatal Pediatric Cases (N=0)

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

4 DISCUSSION

DPV reviewed all serious FAERS reports with Asmanex HFA in pediatric patients less than 18 years of age from January 1, 2017 – July 24, 2023, and identified six serious pediatric 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 Asmanex HFA in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for mometasone furoate inhalation products at this time and will continue routine pharmacovigilance monitoring for Asmanex HFA.

6 REFERENCES

1. Asmanex HFA (mometasone furoate) inhalation aerosol, for oral inhalation use [Prescribing information]. Whitehouse Station, NJ; Merck & Co., Inc.: August, 2019.
2. Asmanex Twisthaler (mometasone furoate inhalation powder) for oral inhalation use [Prescribing information]. Whitehouse Station, NJ; Merck & Co., Inc.: February, 2021.
3. Kalra D. Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review. May 16, 2017. Available at: https://www.fda.gov/media/106983/download

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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