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 Memorandum

<table>
<thead>
<tr>
<th>Date:</th>
<th>January 7, 2015</th>
</tr>
</thead>
</table>
| Safety Evaluator(s): | Kimberley Swank, PharmD  
Division of Pharmacovigilance I |
| Team Leader(s): | Eileen Wu, PharmD  
Division of Pharmacovigilance I |
| Acting Division Director(s): | Robert Levin, MD  
Division of Pharmacovigilance I |
| Product Name(s): | Dymista® (azelastine hydrochloride-fluticasone propionate) |
| Pediatric Labeling Approval Date: | May 1, 2012 |
| Application Type/Number: | NDA 202236 |
| Applicant/Sponsor: | Meda Pharmaceuticals |
| OSE RCM #: | 2014-583 |

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1 INTRODUCTION

This Division of Pharmacovigilance (DPV) memorandum provides and updated FDA Adverse Event Reporting System (FAERS) search as part of the Agency’s effort to prepare for the discussion of Dymista (azelastine hydrochloride-fluticasone propionate) pediatric safety at the March 24, 2015 Pediatric Advisory Committee (PAC) meeting.

Dymista was first approved in 2012 and is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The current approved pediatric labeling is for relief of symptoms of seasonal allergic rhinitis in this same age group.

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for Dymista in pediatric patients. For the September 23, 2014 PAC meeting, DPV searched FAERS for all reports of adverse events from May 1, 2012 through March 31, 2014. One pediatric case of Dymista associated adverse event was identified. Of the one report reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and no deaths directly associated with Dymista use. Dymista was originally categorized under the “designated abbreviated review” process to be reviewed by one of the PAC members prior to the meeting. However, the PAC member recommended that Dymista be moved to the March 24, 2015 meeting to allow all PAC members to provide input.

The updated September 2014 OSE pediatric review is attached.

2 METHODS AND MATERIALS

The FAERS database was searched with the strategy described in Table 1. See Appendix A for a description of the FAERS database.

<table>
<thead>
<tr>
<th>Table 1 FAERS Search Strategy</th>
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<tbody>
<tr>
<td>Date of search</td>
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<tr>
<td>Time period of search</td>
</tr>
<tr>
<td>Product Name(s)</td>
</tr>
<tr>
<td>Search Parameters</td>
</tr>
</tbody>
</table>

*Date since the last Dymista review search (May 1, 2012-March 31, 2014)

3 RESULTS

The updated FAERS search retrieved zero reports.
4 CONCLUSION AND RECOMMENDATIONS

We did not identify any new pediatric safety issues of concern in this review. DPV will continue routine pharmacovigilance monitoring for Dymista.
5 APPENDICES

5.1 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 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).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

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.
Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

Date: June 27, 2014

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Division of Pharmacovigilance (DPV I)
Judy Staffa, Ph.D., R.Ph., Division Director
Division of Epidemiology (DEPI II)

Product Name(s): Dymista® (azelastine hydrochloride-fluticasone propionate)

Pediatric Labeling
Approval Date: May 1, 2012

Application Type/Number: NDA 202236

Applicant/Sponsor: Meda Pharmaceuticals

OSE RCM #: 2014-583

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EXECUTIVE SUMMARY

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for combination drug product azelastine HCl/fluticasone propionate (Dymista®) in pediatric patients.

Azelastine HCl/fluticasone propionate was first approved in 2012 and is indicated for the relief of symptoms of seasonal allergic rhinitis in patients ages 12 years and older.

Over the cumulative time period from May 2012 through March 2014, approximately 857,000 azelastine HCl/fluticasone propionate prescriptions were dispensed and approximately 418,000 patients received dispensed prescriptions for azelastine HCl/fluticasone propionate from U.S. outpatient retail pharmacies. Approximately 5.5% (23,200 patients) of total patients were pediatric patients aged 0-16 years old; of these, pediatric patients aged 0-3 years, 4-11 years, and 12-16 years old accounted for approximately 1%, 30%, and 70%, respectively, of total pediatric patients. “Allergic Rhinitis” was the most common diagnosis associated with the use of azelastine HCl/fluticasone propionate for patients aged 4-11 years, while “Symptoms involving head and neck” was the most common diagnosis associated with the use of azelastine HCl/fluticasone propionate for patients aged 12-16 years. Diagnoses associated with the use of azelastine HCl/fluticasone propionate for patients aged 0-3 years were not captured in the database. Although the use appears to be low, off-label use of azelastine HCl/fluticasone propionate was observed in patients younger than 12 years of age.

The FDA Adverse Event Reporting System (FAERS) was searched for all reports of adverse events from May 1, 2012 through March 31, 2014. We identified one pediatric case of migraine and paresthesia associated with azelastine HCl/fluticasone propionate. This case reported an outcome of other serious (an important medical event that may jeopardize the patient or subject and may require medical or surgical intervention to prevent a serious adverse drug experience). Headache and paresthesia are both listed in the Adverse Reactions section of the current labeling.

This post-marketing evaluation found no evidence of pediatric safety concerns with azelastine HCl/fluticasone propionate. OSE will continue pharmacovigilance monitoring of azelastine HCl/fluticasone propionate.
1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Product Information and Dosing
Azelastine HCl/fluticasone propionate is a H1-antagonist and a corticosteroid nasal spray approved on May 1, 2012 for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older. The safety and efficacy of azelastine HCl/fluticasone propionate have not been established for patients < 12 years of age.

Azelastine HCl/fluticasone propionate is a nasal spray suspension. Each spray delivers 137 mcg of azelastine HCl and 50 mcg of fluticasone propionate. The recommended dose is 1 spray (137 mcg/50 mcg) per nostril twice daily.

Clinical Studies
The efficacy and safety of azelastine HCl/fluticasone propionate was assessed in 3 double-blind, placebo-controlled clinical trials in patients 12 years and older. Patients with seasonal allergic rhinitis were treated with 1 spray per nostril of azelastine HCl/fluticasone propionate nasal spray, azelastine HCl nasal spray, fluticasone nasal spray, or placebo twice a day for 2 weeks. Efficacy was assessed based on the reflective total nasal symptom score (rTNSS). In all 3 trials, azelastine HCl/fluticasone propionate patients had a statistically significant greater decrease in rTNSS as compared to azelastine HCl, fluticasone propionate and placebo. The proportions of subjects reporting adverse reactions were 16 % in the azelastine HCl/fluticasone propionate nasal spray groups, 15 % in the azelastine HCl nasal spray groups, 13 % in the fluticasone nasal spray groups and 12 % in the placebo groups. The most common adverse events that occurred more frequently than placebo in at least 2 % of the patients were dysgeusia, headache, and epistaxis. Somnolence was reported in < 1 % of patients receiving azelastine HCl/fluticasone propionate nasal spray.

In a long-term (12-month) open-label, active-controlled safety trial, patients 12 years of age and older with perennial allergic rhinitis or vasomotor rhinitis were treated with either azelastine HCl/fluticasone propionate nasal spray or fluticasone propionate nasal spray. Overall, adverse events were reported by 47 % of patients treated with azelastine HCl/fluticasone propionate and 44 % of patients treated with fluticasone propionate. The most common adverse events were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis.

1.2 SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS

There are no previous DPV safety reviews.

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1.3  **HIGHLIGHTS OF LABELED SAFETY ISSUES**

Azelastine HCl/fluticasone propionate has no labeled contraindications. Safety concerns described in the Warnings and Precautions section of the labeling include somnolence, local nasal effects, glaucoma, cataracts, immunosuppression, potential reduction in growth velocity in children, use of cytochrome P450 3A4 inhibitors and hypothalamic-pituitary-adrenal (HPA) axis effects.

The most common adverse reactions with a ≥ 2 % incidence in the clinical trials were dysgeusia, headache, pyrexia, cough, nasal congestion, rhinitis, viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea and epistaxis (AR-Clinical Trial Experience).

No formal drug interaction studies have been performed with azelastine HCl/fluticasone propionate nasal spray. The drug interactions of the combination are expected to reflect those of the individual components. Ritonavir and other strong CYP3A4 inhibitors can significantly increase plasma concentrations of fluticasone. Coadministration of azelastine HCl/fluticasone propionate and ritonavir is not recommended. Caution should be used with other potent CYP3A4 inhibitors, such as ketoconazole. Concurrent use of azelastine HCl/fluticasone propionate with alcohol or other central nervous system depressants should be avoided because of somnolence and impairment of central nervous system performance may occur.

Azelastine HCl/fluticasone propionate nasal spray has a pregnancy category C rating and should not be used unless the benefits outweigh the risks.

2  **DRUG UTILIZATION DATA**

2.1  **METHODS AND MATERIALS**

2.1.1  **Determining Settings of Care**

The IMS Health, National Sales Perspectives™ database (see Appendix A for full database description) was used to determine the various retail and non-retail channels of distribution for azelastine HCl/fluticasone propionate. Over the cumulative time period from May 2012 through March 2014, approximately 88% of azelastine HCl/fluticasone propionate packages were distributed to outpatient retail pharmacies; 9% were to mail-order/specialty pharmacies; and 3% were to non-retail settings. As a result, outpatient retail pharmacy utilization patterns were examined. Data from mail-order/specialty and non-retail pharmacy settings were not included in this analysis.

2.1.2  **Data Sources Used**

Proprietary drug utilization databases were used to conduct this analysis (see Appendix A for full database description).

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The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to obtain the nationally estimated number of patients receiving dispensed prescriptions for azelastine HCl/fluticasone propionate, stratified by patient age (0-3, 4-11, 12-16, and 17+ years), from U.S. outpatient retail pharmacies from May 1, 2012 through March 31, 2014, cumulative. The top 10 specialties prescribing azelastine HCl/fluticasone propionate were obtained from the IMS Health, National Prescription Audit™ (NPA) database. The top 5 diagnoses associated with the use of azelastine HCl/fluticasone propionate, stratified by patient age (0-3, 4-11, 12-16, and 17+ years), were obtained from Encuity Research, LLC., Treatment Answers with Pain Panel database.

### 2.2 RESULTS

#### 2.2.1 Patient Demographics

Table 1 below provides the number of patients receiving dispensed prescriptions for azelastine HCl/fluticasone propionate, stratified by patient age, from U.S. outpatient retail pharmacies. Over the cumulative time period from May 2012 through March 2014, approximately 418,000 patients received dispensed prescriptions for azelastine HCl/fluticasone propionate. Adult patients aged 17 years and older accounted for approximately 94.5% (395,000 patients) of total patients receiving dispensed prescriptions for azelastine HCl/fluticasone propionate. Pediatric patients aged 0-16 years old accounted for approximately 5.5% (23,200 patients) of total patients. Of these pediatric patients, the majority of azelastine HCl/fluticasone propionate was dispensed to pediatric patients aged 12-16 years old at approximately 70% (16,200 patients) of total pediatric patients. Pediatric patients aged 0-3 years old (296 patients) and 4-11 years old (6,911 patients) accounted for approximately 1% and 30%, respectively, of total pediatric patients.

<table>
<thead>
<tr>
<th>Patient Age Group</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-16 years</td>
<td>23,160</td>
<td>5.5%</td>
</tr>
<tr>
<td>0 - 3 years</td>
<td>296</td>
<td>1.3%</td>
</tr>
<tr>
<td>4 - 11 years</td>
<td>6,911</td>
<td>29.8%</td>
</tr>
<tr>
<td>12 - 16 years</td>
<td>16,244</td>
<td>70.1%</td>
</tr>
<tr>
<td>17+ years</td>
<td>395,197</td>
<td>94.5%</td>
</tr>
<tr>
<td>Unknown age</td>
<td>376</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Table 1. Nationally estimated number of patients receiving dispensed prescriptions for Dymista®, stratified by patient age*, from U.S. outpatient retail pharmacies, cumulative May 2012 through March 2014


*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands is not advisable and will result in double counting and overestimates of patient counts.

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2.2.2 Prescriber Specialty

Table 2 below provides the number of dispensed prescriptions for azelastine HCl/fluticasone propionate, stratified by the top 10 prescribing specialties, from U.S. outpatient retail pharmacies. Over the cumulative time period from May 2012 through March 2014, approximately 857,000 prescriptions were dispensed for azelastine HCl/fluticasone propionate. Otolaryngologists (241,000 prescriptions) and Allergy/Immunology specialists (236,000 prescriptions) accounted for the highest proportion of total dispensed prescriptions for azelastine HCl/fluticasone propionate at approximately 28% each of total prescriptions dispensed. General Practice/Family Medicine/Doctor of Osteopathic specialists followed at approximately 16% (139,000 prescriptions) of total azelastine HCl/fluticasone propionate dispensed prescriptions. Pediatricians accounted for approximately 2% (15,400 prescriptions) of total azelastine HCl/fluticasone propionate dispensed prescriptions.

<table>
<thead>
<tr>
<th>Prescriber Specialty</th>
<th>Total Dymista®</th>
<th>TRx</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otolarynology</td>
<td>241,094</td>
<td>28.1%</td>
<td></td>
</tr>
<tr>
<td>Allergy/Immunology</td>
<td>236,304</td>
<td>27.6%</td>
<td></td>
</tr>
<tr>
<td>Family Practice/General Practice/Doctor of Osteopathy</td>
<td>138,684</td>
<td>16.2%</td>
<td></td>
</tr>
<tr>
<td>Internal Medicine</td>
<td>75,764</td>
<td>8.8%</td>
<td></td>
</tr>
<tr>
<td>Nurse Practitioner</td>
<td>38,938</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>Physician Assistant</td>
<td>37,419</td>
<td>4.4%</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Diseases</td>
<td>31,291</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>Pediatrician</td>
<td>15,401</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>9,061</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Emergency Medicine</td>
<td>5,981</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>26,827</td>
<td>3.1%</td>
<td></td>
</tr>
</tbody>
</table>


2.2.3 Diagnoses Associated with Use

Diagnoses associated with the use of azelastine HCl/fluticasone propionate, stratified by patient age, from May 2012 through March 2014, cumulative, were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates (Table 3). The number of drug use mentions\(^3\) of azelastine HCl/fluticasone propionate in the pediatric population from office-based physician visits was below the acceptable count allowable to provide a reliable estimate of national use, and should therefore be interpreted with caution.

\(^3\) The term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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“Allergic Rhinitis” (ICD-9 code 477) was the top diagnosis associated with the use of azelastine HCl/fluticasone propionate for pediatric patients aged 4-11 years at approximately 64% of drug uses (21,000 uses, 95% CI <500 – 43,000 uses). For pediatric patients aged 12-16 years, “Symptoms involving head and neck” (ICD-9 code 784) was the top diagnosis associated with the use of azelastine HCl/fluticasone propionate at approximately 53% of drug uses (15,000 uses, 95% CI <500 – 34,000 uses). Azelastine HCl/fluticasone propionate use mentions were not captured for pediatric patients aged 0-3 years.

Table 3. Diagnoses associated with the use of Dymista®, stratified by patient age, as reported from U.S. office-based physician practices, cumulative May 2012 through March 2014

<table>
<thead>
<tr>
<th>Diagnosis Description</th>
<th>Uses</th>
<th>95% CI</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative 5/2012-3/2014</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Dymista®</td>
<td>1,074,000</td>
<td>915,000 - 1,233,000</td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>4-11 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>477 ALLERGIC RHINITIS</td>
<td>33,000</td>
<td>5,000 - 61,000</td>
<td>3.1%</td>
</tr>
<tr>
<td>478 OTH UPRR RESPIRATORY DIS</td>
<td>21,000</td>
<td>&lt;500 - 43,000</td>
<td>64.0%</td>
</tr>
<tr>
<td>381 NONSUPPUR OTITIS MEDIA</td>
<td>11,000</td>
<td>&lt;500 - 27,000</td>
<td>34.0%</td>
</tr>
<tr>
<td><strong>12-16 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>784 SYMPTOMS INVOL HEAD/NECK</td>
<td>28,000</td>
<td>2,000 - 54,000</td>
<td>2.6%</td>
</tr>
<tr>
<td>465 AC URI MULT SITES/NOS</td>
<td>15,000</td>
<td>&lt;500 - 34,000</td>
<td>53.4%</td>
</tr>
<tr>
<td>472 CHR PHARYNG/NASOPHARYNG</td>
<td>6,000</td>
<td>&lt;500 - 18,000</td>
<td>21.5%</td>
</tr>
<tr>
<td>473 CHRONIC SINUSITIS</td>
<td>5,000</td>
<td>&lt;500 - 16,000</td>
<td>17.2%</td>
</tr>
<tr>
<td>995 CERTAIN ADVERSE EFF NEC</td>
<td>2,000</td>
<td>&lt;500 - 8,000</td>
<td>5.8%</td>
</tr>
<tr>
<td><strong>17+ years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>477 ALLERGIC RHINITIS</td>
<td>971,000</td>
<td>820,000 - 1,123,000</td>
<td>90.5%</td>
</tr>
<tr>
<td>473 CHRONIC SINUSITIS</td>
<td>548,000</td>
<td>434,000 - 661,000</td>
<td>56.4%</td>
</tr>
<tr>
<td>478 OTH UPRR RESPIRATORY DIS</td>
<td>134,000</td>
<td>78,000 - 190,000</td>
<td>13.8%</td>
</tr>
<tr>
<td>472 CHR PHARYNG/NASOPHARYNG</td>
<td>73,000</td>
<td>32,000 - 115,000</td>
<td>7.5%</td>
</tr>
<tr>
<td>995 CERTAIN ADVERSE EFF NEC</td>
<td>64,000</td>
<td>25,000 - 103,000</td>
<td>6.6%</td>
</tr>
<tr>
<td><strong>All Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>971,000</td>
<td>44,000</td>
<td>136,000</td>
<td>9.3%</td>
</tr>
<tr>
<td><strong>Unknown Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41,000</td>
<td>10,000</td>
<td>72,000</td>
<td>3.8%</td>
</tr>
</tbody>
</table>


Reference ID: 3683777
3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The FAERS database was searched with the strategy described in Table 3.1.1. See Appendix B for a description of the FAERS database.

<table>
<thead>
<tr>
<th>Table 3.1.1 FAERS Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of search</td>
</tr>
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</tr>
<tr>
<td>Product Name(s)</td>
</tr>
<tr>
<td>Search Parameters</td>
</tr>
</tbody>
</table>

*US approval date

3.2 RESULTS

3.2.1 Total number of FAERS cases by Age

<table>
<thead>
<tr>
<th>Table 3.2.1 Total Adult and pediatric FAERS cases* (May 1, 2012 – March 31, 2014) with azelastine HCl/fluticasone propionate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 years)</td>
</tr>
<tr>
<td>Adults (≥ 17 years)</td>
</tr>
<tr>
<td>Pediatrics (0 - &lt;17 years)</td>
</tr>
</tbody>
</table>

*May include duplicates and transplacental exposures, and have not been assessed for causality
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
§ No additional cases of pediatric deaths were identified among cases not reporting an age.
3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified one pediatric report with an outcome coded as other serious.

Appendix C lists the FAERS case number, FAERS version number and Manufacturer Control Number for the pediatric case.

3.3 SUMMARY OF SERIOUS ADVERSE EVENT REPORTS (N= 1)

The focus of this review is pediatric death and cases of serious adverse events of interest. This review identified one domestic case of migraine and paresthesia that may have been associated with azelastine HCl/fluticasone propionate administration. This case was considered serious because the important medical event, migraine, required evaluation and treatment. We did not identify any new safety issues of concern.

3.3.1 Nervous System Disorder (n = 1)

Labeled Events: Migraine and Paresthesia
Headache: Adverse Reactions – Clinical Trial Experience and Patient Information
Paresthesia: Adverse Reactions – Postmarketing Experience

A 12-year-old female patient reported a migraine three days after taking azelastine HCl/fluticasone propionate for seasonal allergic rhinitis. She also developed tingling after holding her violin and subsequently was not able to hold it. The patient’s past medical history included headache, chronic rhinitis, atopic dermatitis and seasonal allergic rhinitis. Treatment with two unspecified medications was initiated for the migraine. The migraine continued, and dosing of the unspecified medications was increased. The patient was instructed to go to the emergency department where she underwent a CT scan of the head, which was reported as normal. The migraine was considered resolved in April 2013; however, the tingling remained ongoing. Azelastine HCl/fluticasone propionate was discontinued on April 12, 2013.

4 DISCUSSION

The focus of this review is pediatric death and cases of serious adverse events of interest. Of the one report reviewed in pediatric patients, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events and there were no deaths associated with azelastine HCl/fluticasone propionate.

To provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns for azelastine HCl/fluticasone propionate were assessed. The drug utilization analyses in this review indicated that pediatric patients aged 16 years and younger accounted for approximately 5.5% of total patients using azelastine HCl/fluticasone propionate. Although the use appears to be low, the results suggested off-label use of azelastine HCl/fluticasone propionate in patients younger than 12 years of age. Moreover, although infrequent, off-labeled
indications other than allergic rhinitis appear to be mentioned for all pediatric and adult age groups.

Our drug utilization analyses focus on only the outpatient retail pharmacies; therefore, these estimates may not apply to other settings of care such as mail-order/specialty pharmacies and non-retail settings in which azelastine HCl/fluticasone propionate is used.

5 CONCLUSION

There is no evidence from these data that there are specific pediatric safety concerns with azelastine hydrochloride/fluticasone propionate at this time. Although the use appears to be low, off-label use of azelastine HCl/fluticasone propionate was observed in patients younger than 12 years of age.

6 RECOMMENDATIONS

Return to routine pharmacovigilance monitoring.
7 APPENDICES

7.1 APPENDIX A. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

**IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS 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.

The sales data from the IMS Health, National Sales Perspectives™, database do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

**IMS, Vector One®: Total Patient Tracker (TPT)**

The IMS, Vector One®: Total Patient Tracker 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 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

**IMS Health, National Prescription Audit™ (NPA)**

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 80% of retail prescriptions.
dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data are available on-line for 72-rolling months with a lag of 1 month.

**Encuity Research, LLC., TreatmentAnswers™ with Pain Panel**

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

**7.2 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).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.
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.
APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

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Reference ID: 3683777
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLEY A SWANK
01/07/2015

EILEEN WU
01/07/2015

ROBERT L LEVIN
01/07/2015