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**Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review**

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**Product Name(s):** Astepro (azelastine hydrochloride)

**Pediatric Labeling Approval Date:** August 30, 2013 and February 20, 2015

**Application Type/Number:** NDA 022203

**Applicant/Sponsor:** Meda Pharmaceuticals

**OSE RCM #:** 2016-1384

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## **EXECUTIVE SUMMARY**

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing adverse event reports and drug utilization data for azelastine hydrochloride in pediatric patients.

Azelastine is a selective antihistamine, H<sub>1</sub> receptor antagonist, administered as an intranasal spray. Azelastine was originally approved as Astelin nasal spray (NDA 020114) in November 1996 for the treatment of symptoms related to seasonal allergic rhinitis (SAR) in patients 12 years of age and older. Because Astelin had a distinct bitter taste, the sponsor developed a sweetened azelastine intranasal spray, Astepro 0.10% nasal spray (NDA 022203). Astepro 0.10% nasal spray was approved on October 15, 2008 for the relief of symptoms of SAR in patients 12 years of age and older.

A higher strength 0.15% formulation of Astepro as a once-daily dosing regimen for SAR and perennial allergic rhinitis (PAR) was approved on August 14, 2009. On August 30, 2013, the SAR and PAR indications were approved down to the age of 6 years. On February 20, 2015, the SAR indication was approved in pediatric patients 2 through 6 years of age and the PAR indication was approved in pediatric patients aged 6 months to less than 6 years of age.

Drug utilization data for azelastine nasal spray showed pediatric patients aged 0-16 years accounted for approximately 7% of the total use in the U.S. outpatient retail pharmacy setting.

DPV-I identified eight non-serious pediatric cases with azelastine nasal spray in the FDA Adverse Event Reporting System (FAERS) from September 1, 2010 to August 31, 2016. Of the eight non-serious reports reviewed in pediatric patients, there were no new safety signals identified, and no increased severity or frequency of any labeled adverse events.

Based on the review of the pediatric FAERS data for azelastine hydrochloride, no labeling updates are recommended at this time. DPV-I will continue routine monitoring of adverse events with the use of azelastine hydrochloride in pediatric patients.

## **1 INTRODUCTION**

In accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated all postmarketing adverse event reports and drug utilization data for azelastine hydrochloride nasal spray in pediatric patients.

### **1.1 PEDIATRIC REGULATORY HISTORY**

Azelastine is a selective antihistamine, H<sub>1</sub> receptor antagonist, administered as an intranasal spray. Azelastine was originally approved as Astelin nasal spray (NDA 020114) in November 1996 for the treatment of symptoms related to seasonal allergic rhinitis (SAR) in patients 12 years of age and older. Because Astelin had a distinct bitter taste, the sponsor developed a sweetened azelastine intranasal spray, Astepro 0.10% nasal spray (NDA 022203). Astepro 0.10% nasal spray was approved on October 15, 2008 for the relief of symptoms of SAR in patients 12 years of age and older.

The sponsor subsequently filed an application for a higher strength 0.15% formulation as a once-daily dosing regimen for SAR and perennial allergic rhinitis (PAR). This triggered pediatric studies under PREA. In the approval letter issued for Astepro 0.15% nasal spray on August 14, 2009, two post-marketing requirements (PMRs) were defined: PMR 1535-1 was a study of the treatment of PAR and/or SAR to include efficacy and safety assessments for pediatric patients 6 to <12 years of age and PMR 1535-2 was a study of the treatment of PAR and/or SAR to include safety assessments and pharmacokinetic measurements for pediatric patients 6 months to < 6 years of age. On August 30, 2013, based on PMR 1535-1 the SAR and PAR indications were approved down to the age of 6 years. On February 20, 2015, based on PMR 1535-2 the SAR indication was approved in pediatric patients 2 through 6 years of age and the PAR indication was approved in pediatric patients ages 6 months to less than 6 years of age.<sup>1</sup>

### **1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES**

The current Astepro (azelastine hydrochloride) nasal spray product labeling provides the following information excerpted from the pertinent sections.<sup>2</sup>

#### **Indications and Usage**

ASTEPRO is an H<sub>1</sub>-receptor antagonist indicated for the relief of the symptoms of:

- Seasonal allergic rhinitis in patients 2 years of age and older.
- Perennial allergic rhinitis in patients 6 months of age and older.

#### **Warnings and Precautions**

- Somnolence: Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking ASTEPRO
- Avoid concurrent use of alcohol or other central nervous system (CNS) depressants with ASTEPRO because further decreased alertness and impairment of CNS performance may occur

## Adverse Reactions

### *Postmarketing Experience*

During the post approval use of ASTEPRO 0.1% and ASTEPRO 0.15%, the following adverse reactions have been identified. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported include: abdominal pain, atrial fibrillation, blurred vision, chest pain, confusion, disturbance or loss of sense of smell and/or taste, dizziness, dyspnea, facial swelling, hypertension, involuntary muscle contractions, nasal burning, nausea, nervousness, palpitations, paresthesia, parosmia, pruritus, rash, sneezing, insomnia, sweet taste, tachycardia, and throat irritation.

Additionally, the following adverse reactions have been identified during the post approval use of the Astelin brand of azelastine hydrochloride 0.1% nasal spray (total daily dose 0.55 mg to 1.1 mg). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported include the following: anaphylactoid reaction, application site irritation, facial edema, paroxysmal sneezing, tolerance, urinary retention, and xerophthalmia.

### Use in Specific Populations

- **Pediatric Use.** The safety and effectiveness of ASTEPRO have been established for seasonal allergic rhinitis in pediatric patients 2 to 17 years of age and perennial allergic rhinitis in pediatric patients 6 months of age to 17 years of age. The safety and effectiveness of ASTEPRO in pediatric patients below 6 months of age have not been established.

## 2 DRUG UTILIZATION DATA

### 2.1 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct this analysis. **Appendix A** includes detailed descriptions of the databases.

#### 2.1.1 Determining Settings of Care

*The IMS Health, IMS National Sales Perspectives™ database* was used to determine the various settings of care where azelastine hydrochloride solution for nasal spray was distributed by the manufacturers. Sales distribution data for 2015 showed that approximately 79% of all azelastine bottles for nasal administration were sold to U.S. outpatient retail pharmacies, followed by 12% to mail-order/specialty pharmacy settings and 9% to non-retail settings. Based on these results, we examined drug utilization data from only the U.S. outpatient retail pharmacy setting of care.

#### 2.1.2 Data Sources Used

*The IMS, Total Patient Tracker™ (TPT) database* was used to obtain the nationally estimated number of patients who received a prescription for azelastine<sup>1</sup> nasal spray from U.S. outpatient retail pharmacies, stratified by patient age groups (0-1, 2-5, 6-16, 17 years and older) from February 1, 2015<sup>2</sup> through August 31, 2016, cumulative.

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<sup>1</sup>Includes all strengths, brands and generics of azelastine hydrochloride nasal spray formulation.

## 2.2 RESULTS

### 2.2.1 Number of Patients

Table 2.2.1

**Nationally estimated number of patients with a dispensed prescription for azelastine nasal spray, stratified by patient age, from U.S. outpatient retail pharmacies, February 2015 through August 2016**

|                                  | February 1, 2015 - August 31, 2016 |               |
|----------------------------------|------------------------------------|---------------|
|                                  | Patient Count<br>N                 | Share<br>%    |
| <b>azelastine Total Patients</b> | <b>2,165,536</b>                   | <b>100.0%</b> |
| <b>0-16 (age in years)</b>       | <b>152,409</b>                     | <b>7.0%</b>   |
| 0 - 1 years                      | 1,745                              | 1.1%          |
| 2 - 5 years                      | 17,741                             | 11.6%         |
| 6 -16 years                      | 134,260                            | 88.1%         |
| <b>17 years and older</b>        | <b>1,998,420</b>                   | <b>92.3%</b>  |
| <b>Unspecified age</b>           | <b>19,196</b>                      | <b>0.9%</b>   |

Source: IMS, Vector One®: Total Patient Tracker. February 2015 - August 2016. Extracted September 2016.  
File: TPT 2016-1384 azelastine BPCA August 2016.xlsx

Note: includes all strengths (137 mcg, 0.1%, 0.15%) of azelastine nasal spray

<sup>2</sup>Drug utilization data analysis covers start date of February 2015 based on recent approvals of pediatric indications: seasonal allergic rhinitis (SAR) indication was approved in pediatric patients 2 through 6 years of age and the perennial allergic rhinitis (PAR) indication was approved in pediatric patients ages 6 months to less than 6 years of age on February 20, 2015.

### 3 POSTMARKET ADVERSE EVENT REPORTS

#### 3.1 METHODS AND MATERIALS

##### 3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

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

|   |   |
|---|---|
| Date of Search  | September 2, 2016   |
| Time Period of Search   | September 1, 2010* - August 31, 2016                            |
| Search Type   | Product-Manufacturer Reporting Summary                          |
| Product Name(s)   | Product Active Ingredient: azelastine, azelastine hydrochloride |
| Search Parameters   | All ages, all outcomes, worldwide                               |
| * Cut-off date of latest DPV review on azelastine hydrochloride postmarket safety |   |

#### 3.2 RESULTS

##### 3.2.1 Total number of FAERS reports by Age

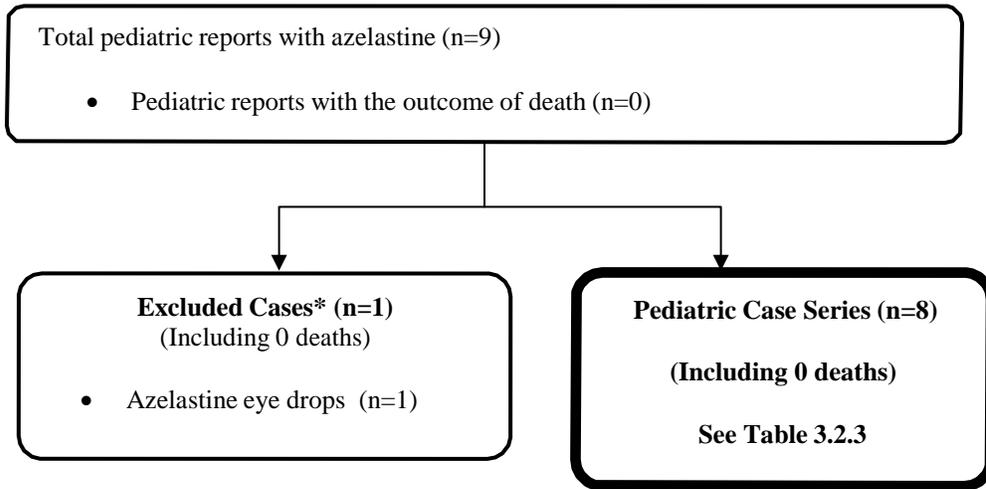
|                                      | <b>All reports (US)</b> | <b>Serious<sup>†</sup> (US)</b> | <b>Death (US)</b> |
|--------------------------------------|-------------------------|---------------------------------|-------------------|
| <b>Adults (&gt; 17 years)</b>        | 1115 (1071)             | 147 (105)                       | 4 (2)             |
| <b>Pediatrics (0 - &lt;17 years)</b> | 9 (9)                   | <b>0 (0)</b>                    | 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, and other serious important medical events.**

##### 3.2.2 Selection of Pediatric Cases in FAERS

We identified 9 non-serious pediatric reports with azelastine (See Table 3.2.1). See **Figure 3.2.2** for the specific selection of cases to be summarized in **Sections 3.3 and 3.4.**

**Figure 3.2.2 Selection of Pediatric Cases with Azelastine**



\* DPV reviewed these cases, but they were excluded from the case series for the reasons listed above **See Table 3.2.3**

**3.2.3 Characteristics of Pediatric Case Series**

Appendix C lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers

| Age (n=8)        | 0 - < 1 month      | 0 |
|------------------|--------------------|---|
|                  | 1 month - <2 years | 0 |
|                  | 2- < 6 years       | 2 |
|                  | 6- <12 years       | 2 |
|                  | 12- < 17 years     | 4 |
| Sex              | Male               | 5 |
|                  | Female             | 3 |
| Country          | United States      | 8 |
|                  | Foreign            | 0 |
| Reported Product | Astepro            | 7 |
|                  | Astelin            | 1 |
| Outcome          | Non-serious        | 8 |
|                  | Serious            | 0 |

**3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)**

There were no pediatric deaths in this case series.

### 3.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=8)

DPV-I identified eight non-fatal pediatric cases with azelastine nasal spray in FAERS from September 1, 2010 to August 31, 2016. Of these eight cases, all were non-serious and six reported labeled adverse events (such as dysgeusia, headache, and cough). Two reports with unlabeled adverse events are described below.

#### **Unlabeled events (n=2)**

No new major safety issues were identified.

#### **Drug ineffective (n=1)**

A 13-year-old male reported lack of relief from his allergy symptoms after receiving azelastine 0.15% nasal spray (one spray per nostril once daily). It was reported that the patient had improper administration technique and the administration instructions were reviewed with the patient. Azelastine therapy was reported as ongoing.

#### **Psychomotor hyperactivity (n=1)**

A 4-year-old male received azelastine 0.15% nasal spray (one spray per nostril once daily) for the treatment of allergies. After initiation of therapy, it was reported that the patient became hyperactive that was described as more active than usual. His therapy was discontinued 6 weeks after initiation of therapy and the event resolved after an unknown time period. Azelastine therapy was reinitiated two months later and the hyperactivity reoccurred and therapy was discontinued again.

*Reviewer comment: The patient received an off-label dosage of Astepro; recommended dosing for children under 5 years of age is azelastine 0.1% one spray per nostril twice daily.*

*Paradoxical stimulation may occasionally occur in children using first-generation antihistamines, especially in higher doses.<sup>3</sup> Although azelastine is not considered to be a first generation antihistamine, the role of improper dosing with azelastine and paradoxical stimulation cannot be disregarded.*

## 4 DISCUSSION

Drug utilization data for azelastine nasal spray showed pediatric patients aged 0-16 years accounted for approximately 7% of the total use in the U.S. outpatient retail pharmacy setting.

Of the eight non-serious reports reviewed in pediatric patients, there were no new safety signals identified, and no increased severity or frequency of any labeled adverse events.

## **5 CONCLUSION**

The review of the eight non-serious azelastine hydrochloride reports in the FAERS database did not suggest adverse events unique to the pediatric population. There were no reports of any pediatric serious (fatal or non-fatal) adverse events for azelastine nasal spray from September 10, 2010 to August 31, 2016. There is no evidence from these data that there are pediatric safety concerns with this drug at this time.

## **6 RECOMMENDATIONS**

Based on the review of the pediatric FAERS data for azelastine hydrochloride, no labeling updates are recommended at this time. DPV-I will continue routine monitoring of adverse events with the use of azelastine hydrochloride in pediatric patients.

## 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.

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

Total Patient Tracker (TPT) 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 2.1 billion prescription claims per year.

## 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).

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.

**7.3 APPENDIX C. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=8)**

| FAERS Case # | FAERS Version # | Manufacturer Control # |
|--------------|-----------------|------------------------|
| 11660207     | 1               | US-MEDA-2011010054     |
| 11660279     | 1               | US-MEDA-2011030126     |
| 11660756     | 1               | US-MEDA-2011080185     |
| 11661268     | 1               | US-MEDA-2012010053     |
| 11661828     | 2               | US-MEDA-2012030156     |
| 11662041     | 1               | US-MEDA-2012080124     |
| 11662492     | 1               | US-MEDA-2013030088     |
| 11796903     | 1               | US-MEDA-2015110098     |

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<sup>1</sup> Donahue K. Azelastine hydrochloride (Astepro) NDA Supplement review. January 28, 2015. DARRTS Reference ID: 3693968

<sup>2</sup> Astepro (azelastine hydrochloride) [package insert]. Somerset, NJ: Meda Pharmaceuticals; February 2015.

<sup>3</sup> Fitzsimons R, van der Poel L, et al. Antihistamine use in children. Arch Dis Child Educ Pract Ed 2015; 100:122–131.

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