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Pediatric Postmarketing Pharmacovigilance Review

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Product Name(s): Dymista (azelastine hydrochloride/fluticasone propionate)

**Pediatric Labeling
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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 (AE) reports with a serious outcome for Dymista (azelastine hydrochloride/fluticasone propionate) nasal spray in pediatric patients.

Azelastine hydrochloride (HCl)/fluticasone propionate nasal spray was first approved in 2012 for the treatment of seasonal allergic rhinitis (SAR) in adults and adolescents 12 years and older. The indication was expanded to include the treatment of SAR in children 6 to 11 years of age in February 2015. The pediatric postmarketing safety profile of azelastine HCl/fluticasone propionate was previously reviewed for the time period of May 1, 2012 to September 30, 2014 and presented at the Pediatric Advisory Committee (PAC) meeting in March 2015; no safety signals were identified and routine pharmacovigilance for all AEs was continued.

The Division of Pharmacovigilance (DPV) evaluated all pediatric postmarketing AE reports with serious outcome for azelastine HCl/fluticasone propionate nasal spray in the FAERS database from October 1, 2014 to July 20, 2017. The start date was chosen to capture all reports from the data lock date of the previous pediatric postmarketing safety profile review for azelastine HCl/fluticasone propionate nasal spray. The review of the FAERS pediatric cases resulted in identification of three non-fatal serious cases containing unlabeled AEs. The three cases reported the unlabeled AEs of dysphagia (n=1), panic attack (n=1), and cellulitis (n=1); however, no new safety signals were identified after review of the cases and AEs for azelastine HCl/fluticasone propionate nasal spray.

The single case of dysphagia contained limited information to determine if the AE was secondary to other labeled AEs for azelastine HCl/fluticasone propionate nasal spray, such as throat discomfort, oropharyngeal edema, or worsening rhinitis with post-nasal drip. For completeness, we searched the FAERS database for additional cases of dysphagia with azelastine HCl/fluticasone propionate nasal spray in the adult population; we retrieved five cases that lacked sufficient information to assess causality (n=3) or reported the occurrence of dysphagia secondary to other labeled AEs such as nasal discomfort, sore throat, and throat dryness and irritation (n=2). We identified one pediatric case of panic attack, which was confounded by use of three concomitant corticosteroids (inhaled n=1, nasal n=2) and resolved after discontinuation of the inhaled corticosteroid; the case did not specify the action taken with azelastine HCl/fluticasone propionate nasal spray or the other nasal corticosteroid. Lastly, the case describing nasal cellulitis may be explained by other labeled AEs (nasal discomfort, facial swelling, immunosuppression) for azelastine HCl/fluticasone propionate nasal spray, which could have led to skin breakdown and increased risk for infection. No new safety signal was identified with azelastine HCl/fluticasone propionate nasal spray. DPV plans to continue postmarketing surveillance of all AEs with azelastine HCl/fluticasone propionate nasal spray.

1 INTRODUCTION

This review evaluated pediatric postmarketing adverse event (AE) reports with a serious outcome for Dymista (azelastine hydrochloride/fluticasone propionate) nasal spray contained in the FDA Adverse Event Reporting System (FAERS) database. This review was triggered by the pediatric labeling date for azelastine hydrochloride (HCl)/fluticasone propionate nasal spray.

1.1 PRODUCT FORMULATION AND INDICATION

Azelastine HCl/fluticasone propionate nasal spray contains an H₁-receptor antagonist and a corticosteroid in a fixed dose containing 0.1% azelastine HCl and 0.037% fluticasone propionate. 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 (total 548 mcg/200 mcg daily).

1.2 PEDIATRIC REGULATORY HISTORY

May 01, 2012: Azelastine HCl/fluticasone propionate was approved in the United States (U.S.) for the treatment of seasonal allergic rhinitis (SAR) in adults and adolescents 12 years of age and older. The approval letter outlined two required studies under the Pediatric Research Equity Act (PREA), postmarketing requirement (PMR) studies 1888-1 and 1888-2.

September 6, 2013: FDA issued a Written Request (WR)^a requesting studies to investigate the potential use of a fixed-dose combination nasal spray of azelastine HCl and fluticasone propionate for the treatment of SAR in children 4 to 11 years of age. The WR outlined two clinical studies (MP 4007 and MP 4008) to be completed and submitted by September 30, 2014 (the two studies correspond to PMR 1888-1 and 1888-2).

June 27, 2014: The Division of Pharmacovigilance (DPV) reviewed the pediatric postmarketing safety profile of azelastine HCl/fluticasone propionate nasal spray for the September 2014 Pediatric Advisory Committee (PAC) meeting. DPV searched the Adverse Event Reporting System (AERS) database from May 1, 2012 (U.S. approval date) through March 31, 2014; DPV identified one pediatric case describing a 12 year-old girl who developed a migraine and paresthesia when holding her violin, 3 days after azelastine HCl/fluticasone propionate use, but concluded there were no new safety signals.¹ The review was categorized under the “designated abbreviated review” process and was reviewed by one of the PAC members prior to the scheduled PAC meeting. The PAC member recommended that azelastine HCl/fluticasone propionate nasal spray be presented at the March 24, 2015 PAC meeting to allow all PAC members to discuss and provide input.

^a The WR requested the Sponsor to conduct an additional clinical study evaluating Astepro (azelastine HCL) nasal spray in a randomized, open-label, parallel group, safety study in children 6 months to less than 6 years of age with PAR and/or SAR for 4 weeks duration.

February 20, 2015: Supplement 008 (S-008) for azelastine HCl/fluticasone propionate nasal spray was approved; the indication for azelastine HCl/fluticasone propionate was extended for use in individuals aged 6 to 11 years old. S-008 contained studies, MP 4007 and MP 4008, which fulfilled the PMRs, PREA requirements, and WR; the studies are described below:

MP 4007: Evaluated the safety of azelastine HCl/fluticasone propionate nasal spray in a 3 month randomized, open label, active control study with fluticasone propionate spray in patients 4 to 11 years of age with allergic rhinitis. The proportion of participants experiencing any treatment-emergent AE was similar in both the azelastine HCl/fluticasone propionate and fluticasone treatment arms and across all age strata.

MP 4008: Evaluated the safety and efficacy of azelastine HCl/fluticasone propionate nasal spray in patients 4 to 11 years of age with moderate to severe SAR through a 2-week randomized, double blind, placebo-controlled study. There was no statistically significant difference between azelastine HCl/fluticasone propionate and placebo for morning and evening 12-hour reflective Total Nasal Symptom Scores (rTNSS), but there was a numerical trend favoring azelastine HCl/fluticasone propionate over placebo for patients 6 to 11 years old. However, data on rTNSS improvement with azelastine HCl/fluticasone propionate was lacking in patients 4 to 5 years old.

January 7, 2015: DPV updated the previous pediatric postmarketing safety profile review of azelastine HCl/fluticasone propionate nasal spray completed June 27, 2014.¹ DPV searched the FAERS database for AEs with azelastine HCl/fluticasone propionate nasal spray from April 1, 2014 through September 30, 2014; this search retrieved zero reports.

March 24, 2015: The results of the azelastine HCl/fluticasone propionate nasal spray pediatric postmarketing safety profile review were presented to the PAC. The recommendation was to continue routine pharmacovigilance for all AEs with azelastine HCl/fluticasone propionate nasal spray.

1.3 HIGHLIGHTS OF LABELED SAFETY ISSUES

5 WARNINGS AND PRECAUTIONS

5.1 Somnolence

In clinical trials, the occurrence of somnolence has been reported in some patients (6 of 853 adult and adolescent patients and 2 of 416 children) taking DYMISTA in placebo controlled trials [*see Adverse Reactions (6.1)*]. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and motor coordination such as operating machinery or driving a motor vehicle after administration of DYMISTA. Concurrent use of DYMISTA with alcohol or other central nervous system depressants should be avoided because additional reductions in alertness and additional impairment of central nervous system performance may occur [*see Drug Interactions (7.1)*].

5.2 Local Nasal Effects

In clinical trials of 2 to 52 weeks' duration, epistaxis was observed more frequently in patients treated with DYMISTA than those who received placebo [see *Adverse Reactions* (6)].

Instances of nasal ulceration and nasal septal perforation have been reported in patients following the intranasal application of corticosteroids. There were no instances of nasal ulceration or nasal septal perforation observed in clinical trials with DYMISTA.

5.3 Glaucoma and Cataracts

Nasal and inhaled corticosteroids may result in the development of glaucoma and/or cataracts. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.4 Immunosuppression

Persons who are using drugs, such as corticosteroids, that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated local or systemic fungal or bacterial infections; systemic viral or parasitic infections; or ocular herpes simplex because of the potential for worsening of these infections.

5.5 Hypothalamic-Pituitary-Adrenal (HPA) Axis Effects

When intranasal steroids are used at higher than recommended dosages or in susceptible individuals at recommended dosages, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of DYMISTA should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy. The concomitant use of intranasal corticosteroids with other inhaled corticosteroids could increase the risk of signs or symptoms of hypercorticism and/or suppression of the HPA axis.

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of withdrawal, e.g., joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

5.7 Effect on Growth

Corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving DYMISTA [see *Use in Specific Populations* (8.4)].

6 ADVERSE REACTIONS

Systemic and local corticosteroid use may result in the following:

- Somnolence [see *Warnings and Precautions* (5.1)]

- Local nasal effects, including epistaxis, nasal ulceration, nasal septal perforation, impaired wound healing, and *Candida albicans* infection [see *Warnings and Precautions* (5.2)]
- Glaucoma and cataracts [see *Warnings and Precautions* (5.3)]
- Immunosuppression [see *Warnings and Precautions* (5.4)]
- Hypothalamic-pituitary-adrenal (HPA) axis effects, including growth reduction [see *Warnings and Precautions* (5.5 and 5.7), *Use in Specific Populations* (8.4)]

6.2 Postmarketing Experience

Cardiac disorders: atrial fibrillation, increased heart rate, palpitations

Eye disorder: blurred vision, cataracts, conjunctivitis, dryness and irritation, eye swelling, glaucoma, increased intraocular pressure, vision abnormal, xerophthalmia

Gastrointestinal disorders: nausea, vomiting

General disorders and administration site condition: aches and pain, application site irritation, chest pain, edema of face and tongue, fatigue, tolerance

Immune system disorders: anaphylaxis/anaphylactoid reactions which in rare instances were severe, hypersensitivity reactions

Musculoskeletal and connective tissue disorders: growth suppression [see *Use in Specific Populations* (8.4)]

Nervous system disorders: disturbance or loss of smell and/ or taste, dizziness, involuntary muscle contractions, paresthesia, parosmia

Psychiatric disorders: anxiety, confusion, nervousness

Renal and urinary disorders: urinary retention

Respiratory, thoracic and mediastinal disorders: bronchospasm, cough, dysphonia, dyspnea, hoarseness, nasal septal perforation, nasal discomfort, nasal dryness, nasal sores, nasal ulcer, sore throat, throat dryness and irritation, voice changes, wheezing

Skin and subcutaneous tissue disorder: angioedema, erythema, face swelling, pruritus, rash, urticaria

Vascular disorder: hypertension

2 POSTMARKET AE REPORTS

2.1 METHODS AND MATERIALS

2.1.1 FAERS Search Strategy

DPV searched the FAERS database with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

Table 2.1.1 FAERS Search Strategy

Date of Search	July 20, 2017
Time Period of Search	October 1, 2014* – July 20, 2017
Search Type	Quick Query Product Manufacturer Reporting Summary

Table 2.1.1 FAERS Search Strategy

Product Active	Azelastine hydrochloride/fluticasone propionate
Ingredient	
Search Parameters	All ages, all outcomes, worldwide
<i>* This start date was chosen because the data lock date of the previous pediatric postmarketing safety profile review for azelastine HCl/fluticasone propionate nasal spray was September 30, 2014.</i>	

2.2 RESULTS

2.2.1 Total Number of FAERS Reports by Age

Table 2.2.1 Total Adult and Pediatric FAERS Reports* from October 1, 2014 to July 20, 2017 with Azelastine HCl/Fluticasone Propionate

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (> 17 years)	328 (307)	44 (24)	0 (0)
Pediatrics (0 - <17 years)	24 (22)	4‡ (2)	0 (0)

*May include duplicates and transplacental exposures, and have not been assessed for causality

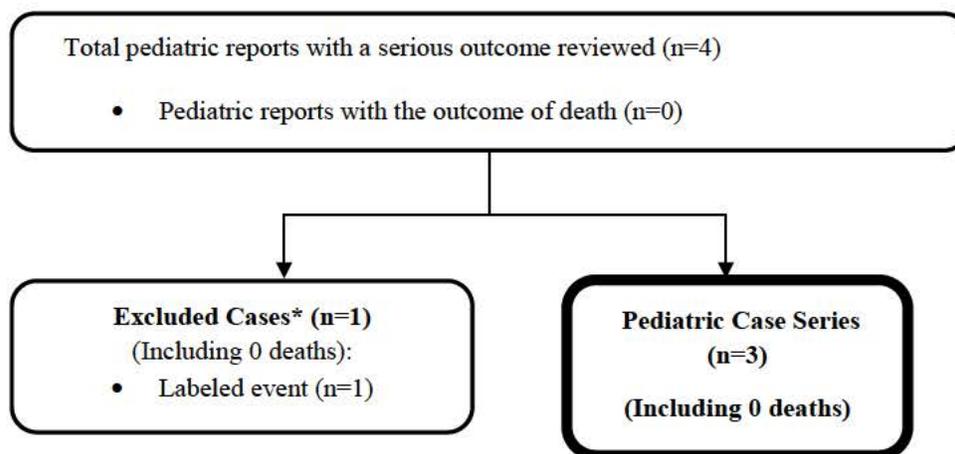
†For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

‡See Figure 3.2.2

2.2.2 Selection of Serious Pediatric Cases in FAERS

We identified four pediatric reports with a serious outcome (See Table 3.2.1). See **Figure 2.2.2** below for the specific selection of cases to be summarized in **Sections 2.3 and 2.4**.

Figure 2.2.2 Selection of Serious Pediatric Cases with azelastine HCl/fluticasone propionate



* DPV reviewed this case, but it was excluded from the case series for the reason listed above

Of the four serious pediatric reports, one report was excluded because it contained the AEs, somnolence and dysphonia, which are labeled in the azelastine HCl/fluticasone propionate nasal spray product label. Somnolence is listed in Warnings and Precautions Section 5.1 and Adverse Reactions Section 6 and 6.1; dysphonia is listed in Adverse Reactions Section 6.2. No change in severity of either labeled AE was noted after review of the report.

2.2.3 Characteristics of Pediatric Case Series

Appendix B lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

Table 2.2.3 Characteristics of Pediatric Case Series with azelastine HCl/fluticasone propionate (N=3)

Age	12- < 17 years	3
Sex	Male	3
Country (n=2)	United States	2
Reported Reason for Use (n=2)	Hay Fever	1
	Allergic Asthma	1
Serious Outcome*	Hospitalized	1
	Other serious	2

* 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. Reports may have more than one outcome.

2.3 SUMMARY OF FATAL PEDIATRIC AE CASES (N=0)

There are no reported deaths in pediatric patients using azelastine HCl/fluticasone propionate from October 1, 2014 through July 20, 2017.

2.4 SUMMARY OF NON-FATAL PEDIATRIC SERIOUS AE CASES (N=3)

Unlabeled Event: Dysphagia

Case 10908656, outcome- other serious important medical events, country unknown, 2015:

A parent reported that her 13-year-old son developed dysphagia two weeks after initiating azelastine HCl/fluticasone propionate nasal spray for treatment of hay fever symptoms. The patient stopped azelastine HCl/fluticasone propionate at an unspecified time and symptoms were improving at the time of report. The patient's concomitant medication included unspecified vitamins.

Reviewer comment: Dysphagia is not a labeled AE for azelastine HCl/fluticasone propionate. However, the case lacks sufficient detail to distinguish dysphagia from other labeled events in the azelastine HCl/fluticasone propionate product label -- throat discomfort (labeled in Adverse Reactions Section 6.2), oropharyngeal edema (labeled in Adverse Reactions Section 6.2), or worsening rhinitis with post nasal drip (labeled in Adverse Reactions Section 6.1).

For completeness, we searched the FAERS database for all reports with azelastine HCl/fluticasone propionate and dysphagia through August 8, 2017 for all ages. The search identified five additional adult reports of dysphagia in association with azelastine HCl/fluticasone propionate use. Of the five adult reports, three lacked sufficient information to assess causality and two reported the occurrence of dysphagia secondary to other events (nasal discomfort, sore throat, and throat dryness and irritation in Adverse Reactions Section 6.2) labeled in the azelastine HCl/fluticasone propionate product label. These cases do not represent a new safety signal.

Unlabeled Event: Panic Attack

Case 13307481, outcome hospitalization, U.S., 2017: A parent reported that her 15-year-old son developed panic attacks a few days after using fluticasone furoate/vilanterol trifenate inhalation, fluticasone nasal spray, and azelastine HCl/fluticasone propionate nasal spray together for treatment of allergic asthma. The patient had a history of an inability to swallow for 6 months and was started on fluticasone furoate/vilanterol trifenate inhalation. A few weeks later, the symptoms did not improve and the patient was started on fluticasone nasal spray and azelastine HCl/fluticasone propionate nasal spray. After a few days of using all medications together, the patient had multiple panic attacks. He was taken to an emergency room twice because of panic attacks. The patient discontinued fluticasone furoate/vilanterol trifenate, but the action taken with fluticasone nasal spray and azelastine HCl/fluticasone propionate nasal spray was unknown. The panic attacks resolved on an unknown date.

Reviewer comment: The patient received three concomitant corticosteroids, which all contain neuropsychiatric events including anxiety in their respective product labels. The simultaneous use of these medications likely potentiated the AEs. Additionally, anxiety is a common psychiatric condition in the pediatric population that typically begins to present in adolescence,² therefore we cannot rule out the possibility that these events occurred secondary to a background medical condition.

Unlabeled Event: Cellulitis

Case 11096141, outcome other serious important medical events, U.S, 2015: A parent reported that her 16-year-old son's nose became "very sore to the touch on the outside and it hurt while blowing," one day after starting azelastine HCl/fluticasone propionate. "There was no pain on the inside of the nose." Azelastine HCl/fluticasone propionate therapy was discontinued three days later. The next morning, the consumer's nose was swollen, red, and hard. When the consumer reached his physician, his whole face was swollen and red with white splotches where the skin was tight. He had no fever or headache. He was diagnosed with cellulitis, which remained ongoing. Treatment information was not provided. The consumer's past medical history included allergies. The patient's concomitant medication included cetirizine.

Reviewer comment: Nasal discomfort and facial swelling are labeled in Adverse Reactions Section 6.2 of the azelastine HCl/fluticasone propionate product label. These events, coupled

with another labeled adverse event, immunosuppression (labeled in Warnings and Precautions Section 5.4, Adverse Reactions Section 6, and Patient Counseling Information Section 17), may explain the mechanism for the development of cellulitis. Nasal and facial swelling and discomfort, leading to breakdown of the skin barrier, could have increased the patient's susceptibility to infection (nasal cellulitis). This singular case does not represent a new safety signal at this time.

3 DISCUSSION

We evaluated all pediatric postmarketing AE reports with a serious outcome for azelastine HCl/fluticasone propionate nasal spray in the FAERS database from October 1, 2014 to July 20, 2017. The start date was chosen to capture all reports from the data lock date of the previous pediatric postmarketing safety profile review for azelastine HCl/fluticasone propionate nasal spray. The review of the FAERS pediatric cases resulted in identification of three non-fatal serious cases containing unlabeled AEs. The three cases reported the unlabeled AEs of dysphagia (n=1), panic attack (n=1), and cellulitis (n=1); however, no new safety signals were identified after review of the cases and AEs for azelastine HCl/fluticasone propionate nasal spray.

The single case of dysphagia contained limited information to determine if the AE was secondary to other labeled AEs for azelastine HCl/fluticasone propionate nasal spray, such as throat discomfort, oropharyngeal edema, or worsening rhinitis with post-nasal drip. For completeness, we searched the FAERS database for additional cases of dysphagia with azelastine HCl/fluticasone propionate nasal spray in the adult population; we retrieved five cases that lacked sufficient information to assess causality (n=3) or reported the occurrence of dysphagia secondary to other labeled AEs, nasal discomfort, sore throat, and throat dryness and irritation (n=2). We identified one pediatric case of panic attack, which was confounded by use of three concomitant corticosteroids (inhaled n=1, nasal n=2) and resolved after discontinuation of the inhaled corticosteroid; the case did not specify the action taken with azelastine HCl/fluticasone propionate nasal spray or the other nasal corticosteroid. Lastly, the case describing nasal cellulitis may be explained by other labeled AEs (nasal discomfort, facial swelling, immunosuppression) for azelastine HCl/fluticasone propionate nasal spray, which could have led to skin breakdown and increased risk for infection.

4 CONCLUSION

There is no evidence from these data that there are pediatric safety concerns with azelastine HCl/fluticasone propionate nasal spray at this time.

5 RECOMMENDATIONS

DPV recommends returning to routine pharmacovigilance monitoring for all AEs with azelastine HCl/fluticasone propionate nasal spray.

6 REFERENCES

1. Swank K. Pediatric Postmarketing Pharmacovigilance Memorandum. January 07, 2015.
See
<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM437534.pdf>
2. Giaconia RM et al. Ages of Onset of Psychiatric Disorders in a Community Population of Older Adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1994;33(5):706-717.

7 APPENDICES

7.1 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).

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 AE 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 AE or medication error in the U.S. population.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR THE PEDIATRIC CASE SERIES WITH DRUG (N=3)

FAERS Case	Version Number	Manufacturer Control Number
10908656	1	2015030013
13307481	1	US-MEDA-2017030007
11096141	1	2015040064

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/s/

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