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Pediatric Postmarketing Pharmacovigilance Review

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xeomin (incobotulinumtoxinA) in pediatric patients <18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with incobotulinumtoxinA in pediatric patients.

The FDA approved Xeomin (incobotulinumtoxinA) on July 30, 2010. It is currently indicated for:

- Chronic sialorrhea in patients 2 years of age and older
- Upper limb spasticity in adults
- Upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
- Cervical dystonia in adults
- Blepharospasm in adults
- Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults

DPV reviewed all U.S. serious FAERS reports with incobotulinumtoxinA in the pediatric population (ages 0 - <18 years) from July 30, 2010, through October 18, 2022, and did not identify any cases for inclusion in a case series.

DPV did not identify any new pediatric safety concerns for incobotulinumtoxinA at this time and will continue to monitor all adverse events associated with the use of incobotulinumtoxinA.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Xeomin (incobotulinumtoxinA) in pediatric patients <18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and the Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with incobotulinumtoxinA in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Xeomin is an acetylcholine release inhibitor and a neuromuscular blocking agent, initially approved for marketing in the United States on July 30, 2010. It is currently indicated for the treatment or improvement of:

- Chronic sialorrhea in patients 2 years of age and older
- Upper limb spasticity in adults
- Upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
- Cervical dystonia in adults
- Blepharospasm in adults
- Temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults

This pediatric postmarketing safety review for incobotulinumtoxinA was stimulated by the pediatric labeling changes represented in Table 1. DPV has not previously presented an evaluation of postmarketing adverse event reports for incobotulinumtoxinA in pediatric patients to the Pediatric Advisory Committee (PAC).

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for IncobotulinumtoxinA		
Date	**Labeling Change**	**Clinical Trial Summary**
August 18, 2020	<u>Upper Limb Spasticity in Pediatric Patients, Excluding Spasticity Caused by Cerebral Palsy</u> Safety and effectiveness have been established in pediatric patients 2 to 17 years of age. The safety and effectiveness of XEOMIN have been established by evidence from adequate and well-controlled studies of XEOMIN in patients 2 to 17 years of age with upper limb spasticity. A pediatric assessment for XEOMIN demonstrates that XEOMIN is safe and effective in another pediatric population. However, XEOMIN is not approved for such patient population due to marketing exclusivity for another botulinum toxin. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.	Study was a prospective, double-blind, dose-response, randomized, multi-center trial with an open-label extension period to evaluate the efficacy and safety of XEOMIN for the treatment of upper limb spasticity in 350 pediatric patients 2 to 17 years of age with upper limb spasticity in one or both upper limbs. Study used a dose-response design, in which the two highest dosages of XEOMIN (8 Units/kg and 6 Units/kg) were compared to the lowest dosage (2 Units/kg), which served as control. In the absence of a placebo control, the efficacy of the 2 Units/kg dosage of XEOMIN could not be evaluated. The co-primary efficacy variables were the change from baseline on the Ashworth Scale for the primary clinical target pattern and the Investigator's Global Impression of Change Scale (GICS), both at Week 4. The change from baseline in Ashworth Scale score was significantly greater for patients treated with XEOMIN 8 Units/kg than for patients treated with XEOMIN 2 Units/kg; the difference in GICS score between patients treated with XEOMIN 8 Units/kg and those treated with XEOMIN 2 Units/kg did not reach statistical significance. However, the clinical meaningfulness of the difference in Ashworth Scale score change between patients treated with XEOMIN 8 Units/kg and those treated with XEOMIN 2 Units/kg was established by a responder analysis. The efficacy of a 6 Units/kg dosage of XEOMIN for the treatment of upper limb spasticity in pediatric patients was not established.[2,3]

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for IncobotulinumtoxinA		
Date	**Labeling Change**	**Clinical Trial Summary**
December 18, 2020	Chronic Sialorrhea in Pediatric Patients The safety and effectiveness of XEOMIN have been established by evidence from an adequate and well-controlled study of XEOMIN in patients 6 to 17 years of age with chronic sialorrhea. Use of XEOMIN in patients 2 to 5 years of age is supported by the findings of efficacy and safety in patients 6 years and older with chronic sialorrhea, and by safety data in patients 2 to 5 years of age. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.	The efficacy and safety of XEOMIN for the treatment of chronic sialorrhea in pediatric patients were evaluated in a prospective, randomized, double-blind, placebo controlled (ages 6-17 years), parallel-group, multicenter trial that enrolled and treated a total of 216 pediatric patients 6-17 years of age with chronic sialorrhea associated with cerebral palsy, other genetic or congenital disorders, or traumatic brain injury. An additional 35 patients 2-5 years of age were treated with open-label XEOMIN in that study. Patients with a body weight <12 kg were excluded. The primary efficacy analysis was conducted in the 6-17 years of age patient group. The co-primary endpoints were the change in unstimulated Salivary Flow Rate (uSFR) and carer's Global Impression of Change Scale (GICS) at Week 4 post-injection. For both the uSFR and GICS, XEOMIN was statistically significantly better than placebo.[4,5]

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Boxed Warning, Contraindications, Warnings and Precautions, Adverse Reactions (from the Highlights of Prescribing Information), and the Pediatric Use sections of the incobotulinumtoxinA product labeling are reproduced below.

----------**BOXED WARNING**----------

WARNING: DISTANT SPREAD OF TOXIN EFFECT

The effects of XEOMIN and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

----------CONTRAINDICATIONS----------

- Known hypersensitivity to the active substance botulinum neurotoxin type A or to any of the excipients
- Infection at the proposed injection sites

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

- Respiratory, speech, or swallowing difficulties: increased risk if bilateral neck muscle injections are needed, or with pre-existing muscular disorders; immediate medical attention may be required
- The potency Units of XEOMIN are not interchangeable with other preparations of botulinum toxin products
- Corneal exposure and ulceration: protective measures may be required
- Risk of ptosis: follow dosage recommendations

----------ADVERSE REACTIONS----------

The most commonly observed adverse reactions at rates specified below and greater than placebo are:

Chronic Sialorrhea
- Chronic Sialorrhea in Adults (≥4% of patients): tooth extraction, dry mouth, diarrhea, and hypertension
- Chronic Sialorrhea in Pediatric Patients (≥1% of patients): bronchitis, headache, and nausea/vomiting

Spasticity:
- Upper Limb Spasticity in Adults (≥2% of patients): seizure, nasopharyngitis, dry mouth, and upper respiratory tract infection
- Upper Limb Spasticity in Pediatric Patients (≥3% of patients): nasopharyngitis and bronchitis

Cervical Dystonia (≥5% of patients): dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain

Blepharospasm (≥10% of patients): eyelid ptosis, dry eye, visual impairment, and dry mouth

Glabellar Lines (>1% of patients): headache

----------USE IN SPECIFIC POPULATIONS----------

8.4 Pediatric Use

Safety and effectiveness of XEOMIN in patients less than 18 years of age have not been established for lower limb spasticity, cervical dystonia, blepharospasm, or glabellar frown lines.

Chronic Sialorrhea in Pediatric Patients
The safety and effectiveness of XEOMIN have been established by evidence from an adequate and well-controlled study of XEOMIN in patients 6 to 17 years of age with chronic sialorrhea. Use of XEOMIN in patients 2 to 5 years of age is supported by the findings of efficacy and safety in patients 6 years and older with chronic sialorrhea, and by safety data in patients 2 to 5 years of age. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Upper Limb Spasticity in Pediatric Patients, Excluding Spasticity Caused by Cerebral Palsy
Safety and effectiveness have been established in pediatric patients 2 to 17 years of age. The safety and effectiveness of XEOMIN have been established by evidence from adequate and well-controlled studies of XEOMIN in patients 2 to 17 years of age with upper limb spasticity. A pediatric assessment for XEOMIN demonstrates that XEOMIN is safe and effective in another pediatric population. However, XEOMIN is not approved for such patient population due to marketing exclusivity for another botulinum toxin. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Juvenile Animal Toxicity Data
In a study in which juvenile rats received intramuscular injections of Xeomin (0, 5, 10, or 30 Units/kg) every other week from postnatal day 21 for 10 weeks, decreased limb use, decreased body weight gain, skeletal muscle atrophy, and decreased bone growth and density were observed at all doses. Male reproductive organ histopathology (atrophy of the germinal epithelium of the testis, associated with hypospermia) was observed at the mid and high doses, and mating behavior was impaired at the high dose. A no-effect dose for adverse effects on development in juvenile animals was not established. The lowest dose tested (5 Units/kg) is less than the human dose of 400 Units on a body weight (kg) basis.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	October 19, 2022
Time period of search	July 30, 2010† - October 18, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: IncobotulinumtoxinA

Table 2. FAERS Search Strategy*	
MedDRA search terms (Version 25.0)	All PTs

* See Appendix A for a description of the FAERS database.
† U.S. approval date for Xeomin (incobotulinumtoxinA)
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from July 30, 2010, through October 18, 2022 with incobotulinumtoxinA.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From July 30, 2010 through October 18, 2022 with IncobotulinumtoxinA			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	881 (698)	266 (97)	24 (14)
Pediatrics (0 - <18 years)	26 (17)	13 **(4)**	5 **(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 U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 4 U.S. serious pediatric reports for incobotulinumtoxinA from July 30, 2010, through October 18, 2022.

No cases were identified for inclusion in a pediatric case series. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded reports from the case series for the following reasons: adverse event was already adequately listed in the product labeling (n=3), or the report was unassessable because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome) or the information is contradictory, or information provided in the case cannot be supplemented or verified (n=1).

3.1.3 Summary of Fatal Pediatric U.S. Cases (N=0)

We did not identify any FAERS U.S. serious fatal pediatric adverse event cases associated with incobotulinumtoxinA in the pediatric population for discussion.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=0)

We did not identify any FAERS U.S. serious, unlabeled, non-fatal adverse event cases associated with incobotulinumtoxinA in the pediatric population.

4 DISCUSSION

DPV reviewed four FAERS U.S. serious reports with incobotulinumtoxinA in the pediatric population (ages 0 - <18 years) from July 30, 2010, through October 18, 2022. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with incobotulinumtoxinA.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for incobotulinumtoxinA at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of incobotulinumtoxinA.

7 REFERENCES

1. Xeomin (incobotulinumtoxinA) [package insert]. Franksville, WI. USA, Merz Pharmaceuticals, LLC. Revised August 2021.

2. U.S Food and Drug Administration. BLA Approval Letter for BLA 125360, Xeomin (incobotulinumtoxinA). August 18, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/125360Orig1s078ltr.pdf (Accessed October 19, 2022).

3 Xeomin (incobotulinumtoxinA) [package insert]. Franksville, WI. USA, Merz Pharmaceuticals, LLC. Revised August 2020.

4. U.S Food and Drug Administration. BLA Approval Letter for BLA 125360, Xeomin (incobotulinumtoxinA). December 18, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/125360Orig1s086,%20s092ltr.pdf (Accessed October 19, 2022).

5. Xeomin (incobotulinumtoxinA) [package insert]. Franksville, WI. USA, Merz Pharmaceuticals, LLC. Revised December 2020.

8 APPENDICES

8.1 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 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 (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.

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