Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	November 14, 2022
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Product Name:	Dysport (abobotulinumtoxinA)
Pediatric Labeling Approval Dates:	September 25, 2019 July 8, 2020
Application Type/Number:	BLA 125274
Applicant:	Ipsen Biopharm Limited
TTT Record ID#:	2022-2191

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dysport (abobotulinumtoxinA) 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 abobotulinumtoxinA in pediatric patients.

The FDA approved Dysport (abobotulinumtoxinA) on April 29, 2009. It is currently indicated for:

- The treatment of cervical dystonia in adults
- The temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults < 65 years of age
- The treatment of spasticity in patients 2 years of age and older

DPV reviewed all U.S. serious FAERS reports with abobotulinumtoxinA in the pediatric population (ages 0 - <18 years) from September 9, 2019 through October 10, 2022 and did not identify any cases for inclusion in a case series.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dysport (abobotulinumtoxinA) 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 abobotulinumtoxinA in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY[1]

Dysport is an acetylcholine release inhibitor and a neuromuscular blocking agent, initially approved for marketing in the United States on April 29, 2009. It is currently indicated for:

- The treatment of cervical dystonia in adults
- The temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults < 65 years of age
- The treatment of spasticity in patients 2 years of age and older

This pediatric postmarketing safety review for abobotulinumtoxinA was stimulated by the pediatric labeling changes represented in Table 1.

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for AbobotulinumtoxinA

Date	Labeling Change	Clinical Trial Summary
September 25, 2019	Upper Limb Spasticity, Excluding Spasticity Caused by Cerebral Palsy Safety and effectiveness have been established in pediatric patients 2 years of age and older. The safety and effectiveness of DYSPORT have been established by evidence from adequate and well-controlled studies of DYSPORT in patients 2 years of age and older with upper limb spasticity. A pediatric assessment for DYSPORT demonstrates that DYSPORT is safe and effective in another pediatric population. However, DYSPORT 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.	The efficacy of DYSPORT for the treatment of upper limb spasticity in pediatric patients 2 years of age and older was evaluated in a double-blind, low-dose controlled, multicenter study (NCT02106351). A total of 208 toxin naive or non-naive patients were enrolled in the modified Intention to Treat population (mITT). The median age of the patients in this study was 9 years (range 2 to 17 years). The primary efficacy endpoint was the mean change from baseline in Modified Ashworth Score in the primary targeted muscle groups and the secondary efficacy endpoint was the mean Physician Global Assessment (PGA) score assessed at Week 6. Although PGA scores numerically favored DYSPORT treatment over the low-dose control, the difference was not statistically significant.[2,3]

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for AbobotulinumtoxinA		
Date	**Labeling Change**	**Clinical Trial Summary**
July 8, 2020	Spasticity Safety and effectiveness have been established in pediatric patients 2 years of age and older. The safety and effectiveness of DYSPORT have been established by evidence from adequate and well-controlled studies of DYSPORT in patients 2 years of age and older with upper and lower limb spasticity. The safety and effectiveness of DYSPORT injected into proximal muscles of the lower limb for the treatment of spasticity in pediatric patients has not been established. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.	This Prior Approval Supplement provides for removal of the exclusion of cerebral palsy patients in the Dysport indication for pediatric patients 2 years of age and older with upper limb spasticity. No additional clinical trial data was obtained.[4,5]

DPV previously evaluated postmarketing adverse event reports with a serious outcome for abobotulinumtoxinA in pediatric patients for the Pediatric Advisory Committee. DPV's evaluation, dated December 16, 2019,[6] was prompted by the pediatric labeling changes on July 29, 2016, which extended the use of abobotulinumtoxinA to the treatment of lower limb spasticity in pediatric patients 2 years of age and older. DPV's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with abobotulinumtoxinA.

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 abobotulinumtoxinA product labeling are reproduced below.

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

WARNING: DISTANT SPREAD OF TOXIN EFFECT

The effects of DYSPORT 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 occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

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

- Hypersensitivity to:
  - any botulinum toxin product or excipients
  - cow's milk protein
- Infection at the proposed injection site(s).

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

- The potency units of DYSPORT are not interchangeable with other preparations of botulinum toxin products
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties
- Recommended dose and frequency of administration should not be exceeded
- Dry eye may occur with glabellar line treatment; if symptoms persist, consider referring patient to an ophthalmologist
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment

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

Most commonly observed adverse reactions are:

Cervical Dystonia
(≥5%): muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain and eye disorders.

Glabellar Lines
(≥2%): nasopharyngitis, headache, injection site pain, injection site reaction, upper respiratory tract infection, eyelid edema, eyelid ptosis, sinusitis, nausea, and blood present in urine.

Spasticity in Adults
- Upper limb spasticity (≥4%): muscular weakness
- Lower limb spasticity (≥5%): falls, muscular weakness, and pain in extremity

Spasticity in Pediatric Patients
- Upper limb spasticity (≥10%): upper respiratory tract infection and pharyngitis
- Lower limb spasticity (≥10%): nasopharyngitis, cough, and pyrexia.

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

8.4 Pediatric Use

Cervical Dystonia
Safety and effectiveness in pediatric patients have not been established.

Glabellar Lines
DYSPORT is not recommended for use in pediatric patients less than 18 years of age.

Spasticity
Safety and effectiveness have been established in pediatric patients 2 years of age and older. The safety and effectiveness of DYSPORT have been established by evidence from adequate and well-controlled studies of DYSPORT in patients 2 years of age and older with upper and lower limb spasticity. The safety and effectiveness of DYSPORT injected into proximal muscles of the lower limb for the treatment of spasticity in pediatric patients has not been established.

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Juvenile Animal Data
In a study in which juvenile rats received a single intramuscular injection of DYSPORT (1, 3, or 10 Units/animal) on postnatal day 21, decreased growth and bone length (injected and contralateral limbs), delayed sexual maturation, and decreased fertility were observed at the highest dose tested, which was associated with excessive toxicity during the first week after dosing.

In a study in which juvenile rats received weekly intramuscular injections of DYSPORT (0.1, 0.3, or 1.0 Units/animal) from postnatal day 21 to 13 weeks of age, decreases in bone mineral content in the injected limb, associated with atrophy of injected and adjacent muscles, were observed at the highest dose tested. No adverse effects were observed on neurobehavioral development. However, dose levels were not adjusted for growth of the pups. On a body weight basis, the doses at the end of the dosing period were approximately 15% of those at initiation of dosing. Therefore, the effects of DYSPORT throughout postnatal development were not adequately evaluate.

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 11, 2022
Time period of search	September 9, 2019† - October 10, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: AbobotulinumtoxinA
MedDRA search terms (Version 25.0)	All PTs

* See Appendix A for a description of the FAERS database.
† Date following the search period in the previous DPV pediatric safety review for abobotulinumtoxinA
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 September 9, 2019, through October 10, 2022 with abobotulinumtoxinA.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From September 9, 2019 through October 10, 2022 with AbobotulinumtoxinA

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	841 (704)	254 (121)	37 (5)
Pediatrics (0 - <18 years)	109 (101)	25 **(17)**	2 **(1)**

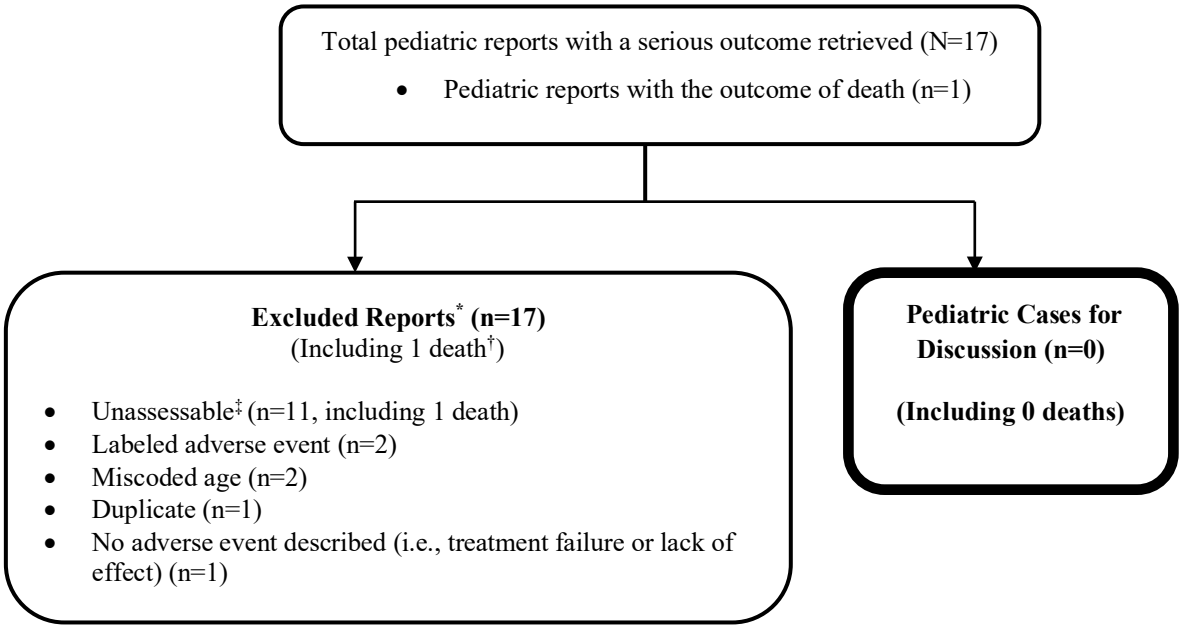
* May include duplicates and transplacental exposures and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 17 U.S. serious pediatric reports for abobotulinumtoxinA from September 9, 2019, through October 10, 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; miscoded age errors (i.e., not a pediatric patient); no adverse event was described in the report; duplicate reports; 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.

Figure 1. Selection of Serious U.S. Pediatric Cases with AbobotulinumtoxinA



* DPV reviewed these reports, but they were excluded from further discussion for the reasons listed above.

† One excluded U.S. FAERS report described a fatal outcome. The patient was a nine-year-old male diagnosed with a major brain injury in the early years of life with several unspecified comorbidities. Parents reported his death when contacted by physician for a refill. Cause of death was not known by reporting physician.

‡ Unassessable: Report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

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 abobotulinumtoxinA 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 abobotulinumtoxinA in the pediatric population.

4 DISCUSSION

DPV reviewed 17 FAERS U.S. serious reports with abobotulinumtoxinA in the pediatric population (ages 0 - <18 years) from September 9, 2019, through October 10, 2022. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with abobotulinumtoxinA.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for abobotulinumtoxinA 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 abobotulinumtoxinA.

7 REFERENCES

1. Dysport (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ. USA, Ipsen Biopharmaceuticals, Inc. Revised July 2020.

2. U.S Food and Drug Administration. BLA Approval Letter for BLA 125274, Dysport (abobotulinumtoxinA). September 25, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/125274Orig1s115ltr.pdf (Accessed October 18, 2022).

3. Dysport (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ. USA, Ipsen Biopharmaceuticals, Inc. Revised September 2019.

4. U.S Food and Drug Administration. BLA Approval Letter for BLA 125274, Dysport (abobotulinumtoxinA). July 8, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/125274Orig1s118ltr.pdf Accessed October 18, 2022).

5. Dysport (abobotulinumtoxinA) [package insert]. Basking Ridge, NJ. USA, Ipsen Biopharmaceuticals, Inc. Revised July 2020.

6. Flowers C. Pediatric Postmarketing Pharmacovigilance Review BLA 125274. Available at: https://www.fda.gov/media/140192/download (Accessed: October 20, 2022)

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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