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 Review

Date:	December 16, 2019
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Product Name(s):	Dysport (AbobotulinumtoxinA)
BLA#	125274
Applicant/Sponsor:	Ipsen Biopharm, LTD
Pediatric Labeling Approval Date:	7/29/2016
OSE RCM #:	2018-1849

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) reports for Dysport (abobotulinumtoxinA) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events reported with Dysport in pediatric patients.

Botulinum toxin type A, the active ingredient in Dysport, is a purified neurotoxin type A complex produced by fermentation of the bacterium *Clostridium botulinum* type A, Hall Strain. Dysport's therapeutic effect is achieved by weakening spastic muscles by selectively blocking the release of acetylcholine at the neuromuscular junction.

FDA first approved Dysport on 4/29/2009 for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients and for the temporary improvements in the appearance of moderate to severe glabellar lines associated with the procerus and corrugator muscle activity. On 10/20/1999, FDA granted Dysport orphan designation for the treatment of lower limb spasticity in pediatric patients with cerebral palsy. On 7/29/2016, FDA approved Dysport for treatment of lower limb spasticity regardless of underlying cause in patients 2 years and older, and on 9/25/2019 for the treatment of upper limb spasticity in patients 2 years and older.

DPV-I reviewed all serious FAERS reports received by FDA from 7/8/2015 through 9/8/2019 with Dysport use in pediatric patients through 17 years of age. We identified three pediatric reports of unlabeled events, including one report describing a fatal outcome. The reported unlabeled events include bronchopneumonia (n=1), blindness (n=1), and gastroparesis (n=1). All three reports were assessed for a drug causal association. The strongest attribute in all three reports in support of a causal association with Dysport use is the temporal relationship (events occurred 2 days, 5 days, and "few days" after Dysport administration). Otherwise, the cases provided limited documentation for adequate causal assessment. DPV-I did not identify similar reports of bronchopneumonia, blindness, or gastroparesis despite an expanded search of the FAERS database and published literature. Consequently, we identified no new safety signals given the paucity of cases and limited case information.

We recommend continued routine pharmacovigilance monitoring of Dysport for adverse events in both adult and pediatric populations.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Dysport (abobotulinumtoxinA) in pediatric patients through age 17 years. The Division of Pharmacovigilance I (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) and Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events reported with Dysport use in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Botulinum toxin type A, the active ingredient in Dysport, is a purified neurotoxin type A complex produced by fermentation of the bacterium *Clostridium botulinum* type A, Hall Strain. Dysport's therapeutic effect is achieved by weakening spastic muscles by selectively blocking the release of acetylcholine at the neuromuscular junction.

Dysport was initially approved on 4/29/2009 for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients and for the temporary improvements in the appearance of moderate to severe glabellar lines associated with the procerus and corrugator muscle activity.[1]

Table 1 summarizes the U.S. approval history of Dysport for pediatric patients ≤ 17 years old.

Table 1. U.S. Approval Dates, Age Group, Indications, and Dosage of Dysport 300 mg and 500 mg Single-Use Dysport[2] Vials for Intramuscular Injection for Pediatric Patients ≤ 17 Years Old

Approval Date	Age Group	Approved Indication	Dosage
10/20/1999 (orphan drug designation)	2 years of age and older	Lower limb spasticity in cerebral palsy	• Unspecified
7/29/2016	2 years of age and older	Lower limb spasticity	• Recommended dosing for lower limb spasticity: 10 Units/kg to 15 Units/kg per limb. Total dose per treatment session must not exceed 15 Units/kg for unilateral lower limb injections, 30 Units/kg for bilateral injections, or 1000 Units, whichever is lower. • The maximum recommended total dose per treatment session is 30 Units/kg or 1000 Units, whichever is lower. Re-treatment, based on return of clinical symptoms, should not occur in intervals of less than 3 months.
9/25/2019	2 years of age and older	Upper limb spasticity	• Recommended dosing for upper limb spasticity, excluding spasticity caused by cerebral palsy: 8 Units/kg to 16 Units/kg per limb. The maximum recommended total dose administered per treatment session must not exceed 16 Units/kg or 640 Units, whichever is lower.

Table 1. U.S. Approval Dates, Age Group, Indications, and Dosage of Dysport 300 mg and 500 mg Single-Use Dysport[2] Vials for Intramuscular Injection for Pediatric Patients ≤ 17 Years Old			
Approval Date	**Age Group**	**Approved Indication**	**Dosage**
			• The maximum recommended total dose per treatment session is 30 Units/kg or 1000 Units, whoever is lower. Re-treatment, based on return of clinical symptoms, should not occur in intervals of less than 3 months.

This review was prompted by the pediatric labeling change on 7/29/2016, that reflected the approval of the indication for the treatment of lower limb spasticity in pediatric patients 2 years of age and older. The initial labeling change identified the indication as specific to pediatric patients with lower limb spasticity caused by cerebral palsy. However, the Division of Neurology I (DN-I) determined the mechanism of action for Dysport was independent of specific disease pathophysiology (i.e., cerebral palsy) and expanded the drug's indication to include pediatric patients regardless of the underlying cause of lower limb spasticity. Dysport received pediatric approval based on the results of five studies including a randomized, multicenter, double-blind, placebo-controlled efficacy study, conducted in 235 pediatric patients, ages 2 to 17 years old, with lower limb spasticity caused by cerebral palsy resulting in dynamic equinus foot deformity. A total of 158 patients were treated with Dysport and 77 were treated with a placebo drug. The most commonly observed adverse reactions from the pediatric studies included upper respiratory tract infection, nasopharyngitis, influenza, pharyngitis, cough and pyrexia.[1] Additionally, adult study results were considered supportive of efficacy for Dysport in the treatment of lower limb spasticity in pediatric patients.[3, 4]

On 9/25/2019, Dysport gained approval for the indication of upper limb spasticity in pediatric patients 2 years and older. At time of initial approval on 4/29/2009, postmarketing requirement 2564-5 (PMR 2564-5) determined that the sponsor would submit safety data assessing distant spread of toxin effects after multiple administrations of Dysport for the treatment of upper and lower limb spasticity, in addition to blood glucose and alkaline phosphatase in pediatric patients ages 2 to 17 years. The sponsor fulfilled PMR 2564-5 with the supplemental biologics license application used to obtain the upper limb spasticity indication.[4]

DPV-I has not previously presented Dysport before the Pediatric Advisory Committee.

1.2 RELEVANT SAFETY LABELING FOR DYSPORT[2]

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that 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 may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. 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 treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose *[see Warnings and Precautions (5.1)]*.

4 CONTRAINDICATIONS

DYSPORT is contraindicated in patients with:

- Known hypersensitivity to any botulinum toxin products, cow's milk protein, or to any of the components in the formulation *[see Warnings and Precautions (5.3)]*. This product may contain trace amounts of cow's milk protein *[see Description (11)]*.
- Infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Toxin Effect

Postmarketing safety data from DYSPORT and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. 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 related to spread of toxin effects**.** The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses and approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than the maximum recommended total dose.

5.2 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of DYSPORT are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

5.3 Hypersensitivity Reactions

Serious hypersensitivity reactions have been reported with DYSPORT. Hypersensitivity reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a serious hypersensitivity reaction occurs, discontinue further injection of DYSPORT and institute appropriate medical therapy immediately.

5.4 Dysphagia and Breathing Difficulties

Treatment with DYSPORT and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved *[see Boxed Warning and Warnings and Precautions (5.2)]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks and require use of a feeding tube to maintain adequate nutrition and

hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports of serious breathing difficulties, including respiratory failure. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Boxed Warning, Warnings and Precautions (5.2), Adverse Reactions (6.1), Clinical Pharmacology (12.2)]*.

5.5 Facial Anatomy in the Treatment of Glabellar Lines

Caution should be exercised when administering DYSPORT to patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in the target muscle(s), marked facial asymmetry, inflammation at the injection site(s), ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin *[see Dosage and Administration (2.4)]* or the inability to substantially lessen glabellar lines by physically spreading them apart *[see Clinical Studies (14.2)]*.

Do not exceed the recommended dosage and frequency of administration of DYSPORT. In clinical trials, subjects who received a higher dose of DYSPORT had an increased incidence of eyelid ptosis.

5.6 Dry Eye with the Treatment of Glabellar Lines

Dry eye has been reported with the use of DYSPORT in the treatment of glabellar lines *[see Adverse Reactions (6.3)]*. Reduced tear production, reduced blinking, and corneal disorders, may occur with use of botulinum toxins, including DYSPORT. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring patient to an ophthalmologist *[see Boxed Warning and Warnings and Precautions 5.2]*.

5.7 Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of DYSPORT *[see Adverse Reactions (6.1)]*.

5.8 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

5.9 Intradermal Immune Reaction

The possibility of an immune reaction when injected intradermally is unknown. The safety of DYSPORT for the treatment of hyperhidrosis has not been established. DYSPORT is approved only for intramuscular injection.

Additional adverse events listed under Section 6 ADVERSE REACTIONS include the following: partial seizures, convulsions, epilepsy, pharyngitis (including pharyngitis streptococcal and pharyngotonsillitis), fatigue, muscular weakness, headache, nausea, infections, and sinusitis.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV-I searched the FAERS database with the strategy described in Table 2. See Appendix A for a description of the FAERS database.

Table 2. FAERS Search Strategy	
Date of search	9/9/2019
Time period of search	7/29/2015* - 9/8/2019
Search type	FDA Business Intelligence Solution (FBIS) Product-Manufacturer Reporting Summary and Quick Query
Product terms	Product active ingredient: AbobotulinumtoxinA Product name: Dysport
Search parameters	All ages, all outcomes, worldwide
* A year prior to the pediatric labeling change.	

2.2 RESULTS

2.2.1 FAERS Data Summary

DPV-I utilized the FAERS search strategy in Table 2 and identified adverse event reports for Dysport. Table 3 presents the FAERS data stratified by pediatrics and adults.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from 7/29/2015 to 9/8/2019 with Dysport			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1053 (849)	324 (147)	14 (8)
Pediatrics (0 - <18 years‡)	92 (73)§	42 (25)§	6 (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, and other serious important medical events.

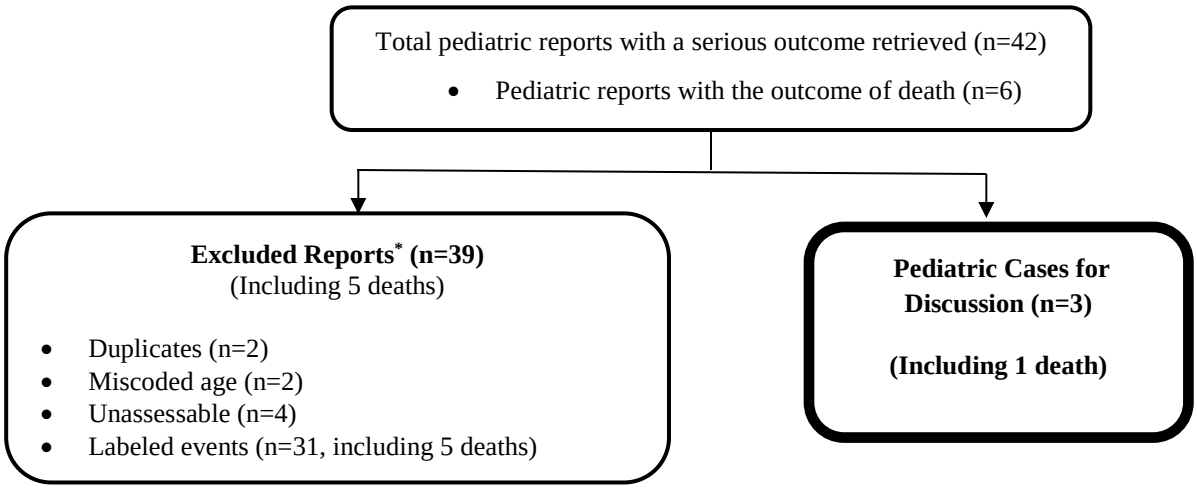
‡ Pediatric clinical studies included patients 17 years of age.

§ One U.S. pediatric death report was identified among reports that did not contain an age. The pediatric report counts reflect this additional report.

2.2.1 Selection of Pediatric Serious Reports in FAERS

The FAERS search retrieved 42 serious pediatric reports for Dysport from 7/29/2015 to 9/8/2019. Figure 1 presents the selection of cases for further discussion.

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



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

DPV-I reviewed all FAERS pediatric reports and excluded 39 reports from further discussion, including 5 reports with fatal outcomes. Reasons for exclusion included duplicate reports (n=2), adult reports miscoded as pediatric (n=2), unassessable due to limited information (n=4), and labeled adverse events (n=31).[a] All labeled events are adequately described in the Dysport product labeling. Five reports describing labeled adverse events were associated with a fatal outcome. Two fatal reports described patients with complex medical histories who received Dysport and were hospitalized for respiratory difficulties and later died from complications of respiratory symptoms and underlying disease; one patient received Dysport then developed dysphagia, aspiration pneumonia, and died in his sleep; one patient with a history of epilepsy developed convulsions one week after receiving Dysport and died; and one case reported the patient developed dyspnea and died after Dysport treatment. All fatal reports lacked additional information.

After exclusions, DPV-I identified 3 reports of serious unlabeled adverse events in pediatric patients with Dysport. The cases are discussed below.

2.2.2 Summary of Fatal Pediatric Adverse Event Report (N=1)

FAERS #1173633, BRA, 2015, described a 3-year-old female with a medical history of chronic encephalopathy and mixed cerebral palsy [spastic; athetoid]. She was admitted to the hospital for a single cycle of Dysport via intramuscular injection into the bilateral gastrocnemius and

[a] Some reports described more than one labeled event. Labeled events included seizure/convulsion (n=11), muscular weakness (n=9), breathing difficulties/dyspnea (n=6), dysphagia (n=5), ptosis (n=3), fatigue (n=3), infection (n=2), sinusitis (n=1), pharyngitis (n=1), headache (n=1), and urinary retention (n=1).

brachial bicep [off-label] muscles. Fenoterol [a beta2-agonist] was administered via intramuscular route to her anterior branch of the left and right obturator nerve, as an anesthetic, before treatment with Dysport. On the same day, she was discharged home. She was crying, and her mom administered dipyrone [a non-steroidal anti-inflammatory]. On day two, she died in her sleep. Her mother reported she saw blood in the child's mouth, but no vomiting. An autopsy determined the cause of death as bronchopneumonia, with generalized visceral congestion, and petechial hemorrhages in the serosae membrane.

Reviewer's comment: This report describes sudden unexpected death with evidence of bronchopneumonia on autopsy. Bronchopneumonia is an unlabeled adverse event for Dysport, and the report provides insufficient information to determine if this was pre-existing or developed after Dysport. Further, it does not contain data to determine if dysphagia or aspiration (labeled) is a plausible alternative explanation for the event, or whether the patient had other underlying risk factors for bronchopneumonia.

2.2.3 Summary of Non-Fatal Pediatric Adverse Event Serious Reports (N=2)

FAERS #13431960, FRA, 2017 described an 11-year-old, male patient. The patient's medical history included previous experience with Botox (onabotulinumtoxinA), administration site pruritus with Botox, Botox induced weakness, spastic paraparesis, and right and left obturator nerve anterior neurotomy. The patient had no concomitant medications. On day one, he received a single cycle treatment with Dysport via intramuscular route at a dose of 820 units for lower limb spasticity. The sites of injection included the right gracilis muscle (110 units, one injection site), left gracilis muscle (110 units, one injection site), right hamstring muscle (300 units, two injection sites, overdose), and left hamstring muscle (300 units, two injection sites, overdose). It was reported that the patient displayed no pre-existing swallowing difficulties or breathing difficulties. On day five after drug injection, he experienced severe blindness, moderate diplopia and moderate retrobulbar headache. Approximately two hours after symptom onset, he recovered from the events. On an unreported day during treatment, brain magnetic resonance imaging, electroencephalogram, and ophthalmological examination were normal. No clinical tests or laboratory tests were performed. On day 20 after drug administration, he again experienced severe blindness, moderate diplopia and moderate retrobulbar headache that resolved after approximately two hours.

Reviewer's comment: The report lacks information to fully characterize the clinical meaning of the reported blindness. Dysport's labeling list known distant spread of toxin effect and "eye disorders" presenting as blurred vision, diplopia, visual acuity reduced, eye pain, eyelid disorder, dry eye, and eye pruritus, which are reported hours to weeks after injection, but not blindness. In this case, blindness, diplopia, and headache occurring on two occasions and lasting 2 hours may be consistent with basilar migraine, and unlikely representative of Dysport's know spread of toxin effects. Of note, Dysport has no dosing recommendations for injecting the hamstring muscles.

FAERS #14352432, USA, 2018 described a 12-year-old, male patient. He had a medical history of allergy to latex, possible lactose allergy, and hospitalization for persistent vomiting. The patient's concomitant medications were not reported. He had previous Botox injections and tolerated them well. On an unspecified date while under treatment, the patient received a single

cycle administration of Dysport at a dose of 500 units, for an unknown indication. The route of the administration, batch number used, and details regarding reconstitution and storage were not reported. On an unspecified date while under treatment, a few days after receiving treatment with Dysport, the patient experienced vomiting and was subsequently hospitalized. The patient was diagnosed with gastroparesis. It was reported that he had no systemic symptoms, no general weakness and no breathing difficulties. The patient received fluids and a gastro-jejunal (GJ) tube as a corrective treatment.

Reviewer's comment: The narrative contains insufficient information to determine if gastroparesis pre-existed Dysport exposure or if the patient was evaluated for other causes of vomiting. Gastroparesis describes signs and symptoms of delayed gastric emptying in the absence of mechanical obstruction due to varied etiologies that affect the complex neuromuscular systems involved in normal gastric motility.[5] *Although Dysport is not specifically labeled for gastroparesis, this clinical outcome may reflect known botulinum toxin effect on gastrointestinal smooth muscles.*

3 DISCUSSION

We identified three pediatric reports of serious unlabeled adverse events in pediatric patients with Dysport from 7/8/2015 to 9/8/2019. The reports described adverse events of bronchopneumonia, blindness, and gastroparesis, respectively; the report of bronchopneumonia was associated with a fatal outcome. All three reports were assessed for a drug causal association. Reports described adverse events that may be consistent with botulinum toxin effect. The strongest attribute in support of drug causal association with Dysport use was the temporal relationship between Dysport exposure and adverse events. However, the cases provided limited documentation for adequate causal assessment. For completeness, we conducted a search of FAERS and published literature for reports of all botulinumtoxinA products associated with either bronchopneumonia, blindness, or gastroparesis in all ages (see Appendix C for search strategies). Neither FAERS nor literature searches identified similar reports. Consequently, we identified no new safety signals.

4 CONCLUSION

DPV-I did not identify any pediatric safety concerns for Dysport at this time.

5 RECOMMENDATIONS

We recommend continued routine pharmacovigilance monitoring of Dysport for adverse events in both adult and pediatric populations.

6 REFERENCES

[1] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/125274s000,125274s001ltr.pdf
[2] Dysport [package insert]. Ipsen Biopharm Ltd., Wrexham, LL13 9UF, UK, Revised 11/2018.
[3] GoldsteinS, Clinical Review BLAs 125274-105: Dysport intramuscular Injection for Lower Limb Spasticity in Pediatric patients. Accessed August 7, 2019 at https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present
[4] PodskalnyG, Cross-Discipline Team Leader Review BLAs 125274-105: Accessed August 7, 2019 at https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present
[5] Camilleri M et al. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013;108(1):18-37.

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 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.

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

#	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age	Sex	Country Derived	Serious Outcome(s)*
1	11/13/2015	11736333	1	BR-Ipsen Biopharmaceuticals, Inc.-2015-08518	Expedited	3 YR	Female	BRA	DE
2	4/12/2017	13431960	2	FR-Ipsen Biopharmaceuticals, Inc.-2017-02985	Expedited	12 YR	Male	FRA	OT
3	1/4/2018	14352432	2	US-Ipsen Biopharmaceuticals, Inc.-2018-00018	Expedited	12 YR	Male	USA	HO

Abbreviations: DE=Death, HO=Hospitalization, OT= Other serious important medical event, and non-serious, BRA = Brazil, FRA = France, USA = United States of America.

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience.

7.3 APPENDIX C. ADDITIONAL FAERS AND LITERATURE SEARCHES

Table 4. FAERS Search Strategy	
Date of search	09/09/2019
Time period of search	All reports through 9/8/2019
Search type	FBIS Product-Manufacturer Reporting Summary
Product terms	Product name: Dysport, Xeomin, Botox, and Botox Cosmetic; Active ingredient: Botulinum toxin NOS, and botulinum toxin type A
Search #1	Bronchopneumonia (Preferred term)
Search #2	Blindness (Preferred term)
Search #3	Impaired gastric emptying (Preferred term)
MedDRA version	22.0
Search parameters	All ages, all outcomes, worldwide

Table 5. Literature Search Strategy	
Date of search	9/9/2019
Database	EMBASE; PubMed@FDA
Drug name	('botulinum toxin a'/exp OR 'botulinum toxin a')
Search #1	("botulinum toxins"[MeSH Terms] OR ("botulinum"[All Fields] AND "toxins"[All Fields]) OR "botulinum toxins"[All Fields] OR ("botulinum"[All Fields] AND "toxin"[All Fields]) OR "botulinum toxin"[All Fields]) AND ("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields])
Search #2	("botulinum toxins"[MeSH Terms] OR ("botulinum"[All Fields] AND "toxins"[All Fields]) OR "botulinum toxins"[All Fields] OR ("botulinum"[All Fields] AND "toxin"[All Fields]) OR "botulinum toxin"[All Fields]) AND ("blindness"[MeSH Terms] OR "blindness"[All Fields])
Search #3	("botulinum toxins"[MeSH Terms] OR ("botulinum"[All Fields] AND "toxins"[All Fields]) OR "botulinum toxins"[All Fields] OR ("botulinum"[All Fields] AND "toxin"[All Fields]) OR "botulinum toxin"[All Fields]) AND ("gastroparesis"[MeSH Terms] OR "gastroparesis"[All Fields])
Years included in search	All years

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/s/

CHARLENE M FLOWERS
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