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 7, 2022
Safety Evaluator:	Debra Ryan, PharmD, MBA Division of Pharmacovigilance I (DPV-I)
Medical Officer:	Ivone Kim, MD DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, PhD DPV-I
Division Director:	Cindy Kortepeter, PharmD DPV-I
Product Name:	Botox (OnabotulinumtoxinA)
Pediatric Labeling Approval Dates:	September 12, 2018 June 20, 2019 October 18, 2019 July 8, 2020 February 9, 2021
Application Type/Number:	BLA 103000
Applicant:	Allergan
TTT Record ID#:	2022-624

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Botox (onabotulinumtoxinA) 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) Pediatric Research Equity Act (PREA). This review focuses on U.S. serious unlabeled adverse events associated with onabotulinumtoxinA in pediatric patients.

The FDA approved Botox (onabotulinumtoxinA) on December 9, 1991. It is currently indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication.
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).
- Treatment of spasticity in patients 2 years of age and older.
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain.
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients.
- Treatment of blepharospasm associated with dystonia in patients 12 years of age and older.
- Treatment of strabismus in patients 12 years of age and older.

DPV reviewed all U.S. serious FAERS reports with onabotulinumtoxinA in the pediatric population (ages 0 - <18 years) from December 9, 1991, through June 15, 2022, and did not identify any cases for inclusion in a case series.

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

1 INTRODUCTION

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

1.1 PEDIATRIC REGULATORY HISTORY[1]

Botox is an acetylcholine release inhibitor and a neuromuscular blocking agent, initially approved for marketing in the U.S. on December 9, 1991. It is currently indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication.
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).
- Treatment of spasticity in patients 2 years of age and older.
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain.
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients.
- Treatment of blepharospasm associated with dystonia in patients 12 years of age and older.
- Treatment of strabismus in patients 12 years of age and older.

Table 1 shows the pediatric labeling changes pursuant to PREA for onabotulinumtoxinA.

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

Date	Labeling Change	Clinical Trial Summary
September 12, 2018	*Prophylaxis of Headaches in Chronic Migraine* Safety and effectiveness in patients below the age of 18 years have not been established.	123 adolescent patients (ages 12 to <18 years) with chronic migraine were randomized to receive Botox 74 Units, Botox 155 Units, or placebo, for one injection cycle. This trial did not establish the efficacy of Botox, compared with placebo, for the prophylaxis of headaches in adolescents with chronic migraine.[2,3]

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for OnabotulinumtoxinA		
Date	**Labeling Change**	**Clinical Trial Summary**
June 20, 2019	*Upper Limb Spasticity* Safety and effectiveness for the treatment of upper limb spasticity have been established in pediatric patients 2 to 17 years of age. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.	The efficacy and safety of BOTOX for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 1 (NCT01603602), a randomized, multi-center, double-blind, placebo-controlled study. Study 1 included 234 pediatric patients with upper limb spasticity because of cerebral palsy or stroke. A total dose of 3 Units/kg BOTOX (maximum 100 Units), 6 Units/kg BOTOX (maximum 200 Units), or placebo was injected intramuscularly and divided between the elbow or wrist and finger muscles. Patients were followed for 12 weeks after injection. Compared to placebo, significant improvements from baseline were observed at all timepoints for BOTOX-treated patients.[4,5]
October 18, 2019	*Lower Limb Spasticity, 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 BOTOX have been established by evidence from adequate and well-controlled studies of BOTOX in patients 2 to 17 years of age with lower limb spasticity.	The efficacy and safety of BOTOX for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 2 (NCT01603628), a randomized, multi-center, double-blind, placebo-controlled study. Study 2 included 381 pediatric patients with lower limb because of cerebral palsy. A total dose of 4 Units/kg BOTOX (maximum 150 Units), 8 Units/kg BOTOX (maximum 300 Units), or placebo was injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior. Patients were followed for 12 weeks after injection. Statistically significant differences between BOTOX and placebo were demonstrated for the 8 Units/kg dose only. Spasticity caused by cerebral palsy was excluded because of unexpired exclusivity granted to Ipsen for Dysport for this indication.[6,7]
July 8, 2020	*Spasticity* The safety and effectiveness of BOTOX have been established by evidence from adequate and well-controlled studies of BOTOX in patients 2 to 17 years of age with upper and lower limb spasticity.	The agreement between two Applicants to waive the unexpired orphan exclusivity for their respective products allowed the exclusion of spasticity caused by cerebral palsy to be removed from the product labeling.[8,9] No additional clinical trial data was obtained.

Table 1. Pediatric Labeling Changes and Clinical Trial Summary for OnabotulinumtoxinA		
Date	**Labeling Change**	**Clinical Trial Summary**
February 9, 2021	*Detrusor Overactivity associated with a Neurologic Condition* Safety and effectiveness for detrusor overactivity associated with a neurologic condition have been established in pediatric patients 5 years and older who have an inadequate response to or are intolerant of anticholinergic medication.	Study 191622-120 (NCT01852045) was a multicenter, randomized, double-blind, parallel-group clinical study conducted in patients 5 to 17 years of age with urinary incontinence due to detrusor overactivity associated with a neurologic condition. A total of 113 patients who had an inadequate response to or were intolerant of at least one anticholinergic medication were enrolled. Patients were randomized to Botox 50 Units, 100 Units or 200 Units, not to exceed 6 Units/kg body weight. The study results demonstrated within group improvements in the primary efficacy variable of change from baseline in daytime urinary incontinence episodes (normalized to 12 hours) at the primary efficacy time point (Week 6) for all 3 BOTOX treatment groups.[10,11]

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

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 onabotulinumtoxinA product labeling are reproduced below.

----------BOXED WARNING----------

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX 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, 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 an underlying condition 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 those used to treat cervical dystonia and spasticity and at lower doses.

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

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation
- Infection at the proposed injection site
- Intradetrusor Injections: Urinary tract infection or urinary retention

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

- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur
- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products.
- Potential serious adverse reactions after BOTOX injections for unapproved uses
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment
- Use with caution in patients with compromised respiratory function
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus
- Bronchitis and upper respiratory tract infections in patients treated for spasticity
- Urinary tract infections in patients treated for OAB
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or adult detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus.

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

- The most common adverse reactions (≥5% and >placebo, if applicable) are:
- OAB: urinary tract infection, dysuria, urinary retention
- Pediatric Detrusor Overactivity associated with a neurologic condition: urinary tract infection, leukocyturia, bacteriuria
- Chronic Migraine: neck pain, headache
- Pediatric Spasticity: upper respiratory tract infection
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

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

8.4 Pediatric Use

Overactive Bladder
Safety and effectiveness in patients below the age of 18 years have not been established.

Detrusor Overactivity associated with a Neurologic Condition
The safety and effectiveness of BOTOX for detrusor overactivity associated with a neurologic condition have been established in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication. Use of BOTOX in this patient population is based on the results of a randomized, double-blind, parallel group trial in 113 pediatric patients 5 to 17 years of age (inclusive) with detrusor overactivity associated with a neurologic condition (Study 191622-120) and a long-term, multicenter, double-blind, long-term extension trial (Study 191622-121). The most common adverse reactions in this population were urinary tract infection, bacteriuria, hematuria, and leukocyturia.

The safety and effectiveness of BOTOX have not been established in patients with NDO younger than 5 years of age.

Prophylaxis of Headaches in Chronic Migraine
Safety and effectiveness in patients below the age of 18 years have not been established.

In a 12-week, multicenter, double-blind, placebo-controlled clinical trial, 123 adolescent patients (ages 12 to below 18 years) with chronic migraine were randomized to receive BOTOX 74 Units, BOTOX 155 Units, or placebo, for one injection cycle. This trial did not establish the efficacy of BOTOX, compared with placebo, for the prophylaxis of headaches in adolescents with chronic migraine.

Spasticity
Safety and effectiveness have been established in pediatric patients 2 to 17 years of age. The safety and effectiveness of BOTOX have been established by evidence from adequate and well-controlled studies of BOTOX in patients 2 to 17 years of age with upper and lower limb spasticity.

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 intramuscular injection of BOTOX (0, 8, 16, or 24 Units/kg) every other week from postnatal day 21 for 12 weeks, changes in bone size/geometry associated with decreased bone density and bone mass were observed at all doses, in association with limb disuse, decreased muscle contraction, and decreased body weight gain. Impairment of fertility and male reproductive organ histopathology (degeneration of seminiferous tubules of the testis) were observed at the mid and high doses. Bone and male reproductive organ effects showed evidence of reversibility after dosing cessation. The no-effect dose for adverse

developmental effects in juvenile animals (8 Units/kg) is similar to the human dose (400 Units) on a body weight (kg) basis.

Axillary Hyperhidrosis
Safety and effectiveness in patients below the age of 18 years have not been established.

Cervical Dystonia
Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

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	June 16, 2022
Time period of search	December 9, 1991† - June 15, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	Product Active Ingredient: OnabotulinumtoxinA
MedDRA search terms (Version 25.0)	All PTs
* See Appendix A for a description of the FAERS database. † U.S. approval date for Botox (onabotulinumtoxinA) 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 December 9, 1991, through June 15, 2022 with onabotulinumtoxinA.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From December 9, 1991 through June 15, 2022 with OnabotulinumtoxinA			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	21,274 (20,002)	3,958 (2,810)	375 (270)
Pediatrics (0 - <18 years)	620 (353)	438 **(183)**	161‡ **(46)**

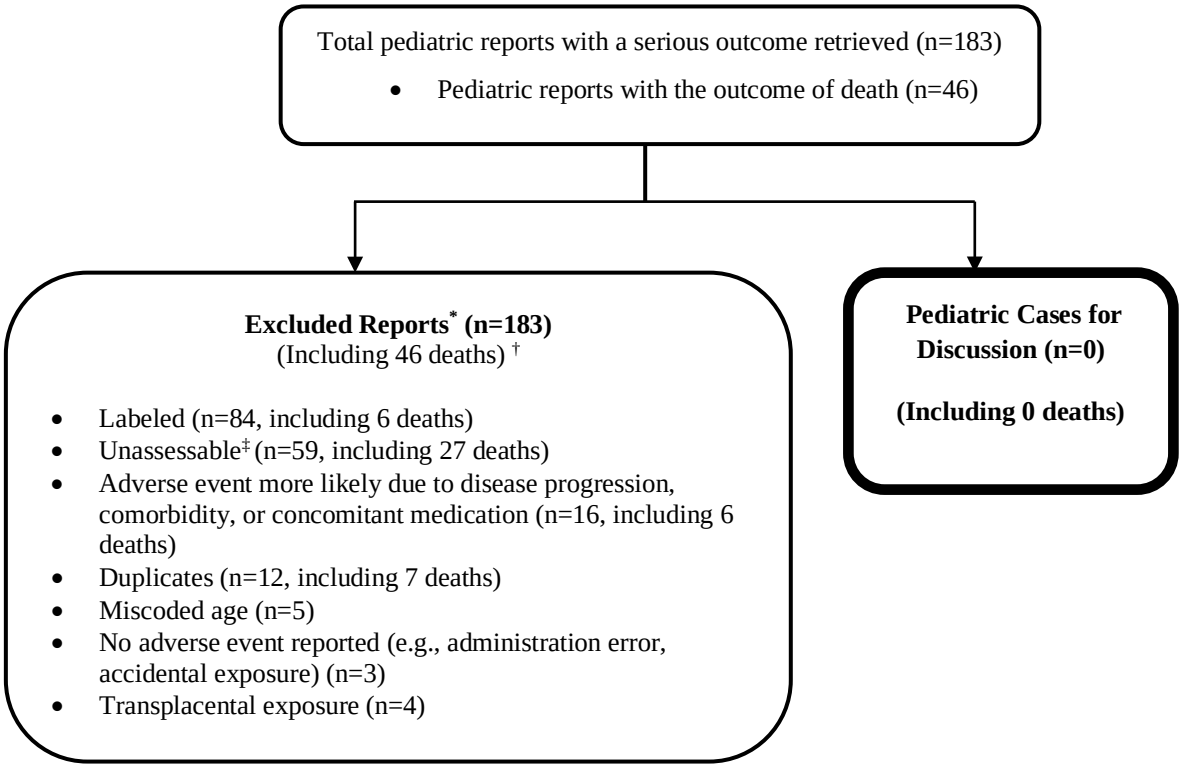
* May include duplicates and transplacental exposures and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ Forty-one reports of pediatric deaths were identified among reports not reporting an age. These reports are reflected in the counts of pediatric reports.

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

Our FAERS search retrieved 183 U.S. serious pediatric reports for onabotulinumtoxinA from approval on December 9, 1991, through June 15, 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 various reasons, such as if the adverse event was already adequately listed in the product labeling; or the reported adverse events were more likely due to disease progression, comorbidity, or concomitant medication; miscoded age errors (i.e., not a pediatric patient); no adverse event was described in the report; duplicate reports; reports of transplacental exposure; 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 OnabotulinumtoxinA



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

† Forty-six excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to onabotulinumtoxinA. These reports were excluded for the following reasons: the report did not provide sufficient clinical detail to assess causality (n=27); the report is a duplicate (n=7); the report describes a labeled adverse event (respiratory arrest (n=5) and seizure (n=1)); the adverse event is secondary to exacerbation or complications of the underlying medical condition (n=6). These six fatal reports described events in pediatric patients with complex medical histories. 1) A 16-year-old male with quadriplegic infantile cerebral palsy and congenital hydrocephalus with cause of death attributed on autopsy to ischemic bowel due to abdominal adhesions from multiple surgeries; 2) A six-year-old female with hydranencephaly and severe spastic quadriplegic cerebral palsy who developed staphylococcus aureus pneumonia and subsequently died of respiratory failure and hypovolemic shock; 3) A four-year-old male with an unknown etiology for disability "(cerebral palsy being best classification at the time)" and severe seizures (6-12/day) who developed staphylococcus/pseudomonas pneumonia. His mother reported his death with specifics unknown; 4) A 15-year-old male with complicated spina bifida (myelomeningocele) to the lower spinal cord, chiari malformation, and dextrocardia with death attributed to multiple emboli to the brain secondary to coagulopathy of unknown etiology or deep vein thrombosis from manipulation of lower extremities; 5) A two-year-old female who was described as a "severely involved kid (trached, G-tube, tone so severe she dislocated both hips, fractured her own femur and was causing foot deformities 6 months after her near-death from anoxia)" and who had been discharged to hospice care with limited life expectancy prior to receiving onabotulinumtoxinA for palliative care. Patient died from respiratory arrest; 6) A 14-year-old female involved in a motor vehicle accident and cause of death was unconfirmed but suspected to be due to a fatal arrythmia.

‡ 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) or 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 fatal pediatric adverse event cases associated with onabotulinumtoxinA 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 onabotulinumtoxinA in the pediatric population.

4 DISCUSSION

DPV reviewed 183 FAERS U.S. serious reports with onabotulinumtoxinA in the pediatric population (ages 0 - <18 years) from December 9, 1991, through June 15, 2022. We identified no new safety signals, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with onabotulinumtoxinA.

5 CONCLUSION

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

7 REFERENCES

1. Botox (onabotulinumtoxinA) [package insert]. Madison, NJ. USA, Allergan USA, Inc. Revised August 2022.

2. U.S Food and Drug Administration. BLA Approval Letter for BLA 103000, Botox (onabotulinumtoxinA). September 12, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/103000Orig1s5308ltr.pdf (Accessed October 5, 2022).

3. Botox (onabotulinumtoxinA) [package insert]. Irvine, CA. Allergan, Inc. Revised September 2018.

4. U.S Food and Drug Administration. BLA Approval Letter for BLA 103000, Botox (onabotulinumtoxinA). June 20, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/103000Orig1s5309ltr.pdf (Accessed October 5, 2022).

5. Botox (onabotulinumtoxinA) [package insert]. Madison, NJ. USA, Allergan USA, Inc. Revised June 2019.

6. U.S Food and Drug Administration. BLA Approval Letter for BLA 103000, Botox (onabotulinumtoxinA). October 18, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/103000Orig1s5310ltr.pdf (Accessed October 5, 2022).

7. Botox (onabotulinumtoxinA) [package insert]. Madison, NJ. USA, Allergan USA, Inc. Revised October 2019.

8. U.S Food and Drug Administration. BLA Approval Letter for BLA 103000, Botox (onabotulinumtoxinA). July 8, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/103000Orig1s5315ltr.pdf (Accessed October 5, 2022).

9. Botox (onabotulinumtoxinA) [package insert]. Madison, NJ. USA, Allergan USA, Inc. Revised July 2020.

10. U.S Food and Drug Administration. BLA Approval Letter for BLA 103000, Botox (onabotulinumtoxinA). February 9, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/103000Orig1s5318ltr.pdf (Accessed October 5, 2022).

11. Botox (onabotulinumtoxinA) [package insert]. Madison, NJ. USA, Allergan USA, Inc. Revised February 2021.

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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARMEN CHENG on behalf of DEBRA L RYAN
11/07/2022 12:41:19 PM

IVONE E KIM
11/07/2022 01:01:23 PM

CARMEN CHENG
11/07/2022 01:36:29 PM

CINDY M KORTEPETER
11/07/2022 02:04:19 PM