CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

103000Orig1s5320

Trade Name:	BOTOX
Generic or Proper Name:	OnabotulinumtoxinA
Sponsor:	Allergan INC
Approval Date:	July 28, 2021
Indication:	BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent 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

CENTER FOR DRUG EVALUATION AND RESEARCH

103000Orig1s5320

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	**X**
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

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103000Orig1s5320

APPROVAL LETTER

BLA 103000/S-5320

SUPPLEMENT APPROVAL

Allergan, Inc.
Attention: Darshana Malavade, MS
Director, Regulatory Affairs
2525 Dupont Drive, AND200A
Irvine, CA 92612

Dear Ms. Malavade:

Please refer to your supplemental biologics license application (sBLA), dated September 28, 2020, received September 28, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for Botox (onabotulinumtoxinA) injection.

This Prior Approval supplemental biologics application provides for the addition of dosing guidance for 8 additional upper limb muscles within the approved muscle groups for the adult upper limb spasticity indication for Botox.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Taura Holmes, PharmD, MS, Senior Regulatory Project Manager, at Taura.Holmes@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

ERIC P BASTINGS
07/28/2021 07:33:53 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103000Orig1s5320

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BOTOX safely and effectively. See full prescribing information for BOTOX.

BOTOX® (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use
Initial U.S. Approval: 1989

WARNING: DISTANT SPREAD OF TOXIN EFFECT
See full prescribing information for complete boxed warning.
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 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 an underlying condition that would predispose them to these symptoms. (5.1)

RECENT MAJOR CHANGES

Indications and Usage, Pediatric Detrusor Overactivity associated with a Neurologic Condition (1.2)	2/2021
Dosage and Administration, Pediatric Detrusor Overactivity associated with a Neurologic condition (2.4)	2/2021
Dosage and Administration, Adult Spasticity (2.6)	7/2021

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent 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 (1.1)
- 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 (1.1)
- 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. (1.2)
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1 3)
- Treatment of spasticity in patients 2 years of age and older (1.4)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.5)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.6)
- Treatment of blepharospasm associated with dystonia in patients 12 years of age and older (1.7)
- Treatment of strabismus in patients 12 years of age and older (1.7)

Limitations of Use

Safety and effectiveness of BOTOX have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.6)

DOSAGE AND ADMINISTRATION

- Follow indication-specific dosage and administration recommendations. In a 3 month interval, do not exceed a total dose of:
  - Adults: 400 Units
  - Pediatrics: the lesser of 10 Units/kg or 340 Units (2.1)
- See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)
- Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)
- Adult Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)
- Pediatric Detrusor Overactivity associated with a Neurologic Condition: 0.5 mL injections across 20 sites into the detrusor (2.4)
  - Greater than or equal to 34 kg: Recommended total dose is 200 Units
  - Less than 34 kg: Recommended total dose is 6 Units/kg
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.5)
- Adult Upper Limb Spasticity: Recommended total dose up to 400 Units divided among affected muscles (2.6)
- Adult Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.6)
- Pediatric Upper Limb Spasticity: Recommended total dose 3 Units/kg to 6 Units/kg (maximum 200 Units) divided among affected muscles (2.7)
- Pediatric Lower Limb Spasticity: Recommended total dose 4 Units/kg to 8 Units/kg (maximum 300 Units) divided among affected muscles (2.7)
- Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients (2.8)
- Axillary Hyperhidrosis: 50 Units per axilla (2.9)
- Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.10)
- Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX (2.11)

DOSAGE FORMS AND STRENGTHS

For Injection: 50 Units, 100 Units or 200 Units vacuum-dried powder in a single-dose vial (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4, 5.4, 6)
- Infection at the proposed injection site (4)
- Intradetrusor Injections: Urinary tract infection or urinary retention (4)

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 (5.1, 5.6)
- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.2, 11)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- 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. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and >placebo, if applicable) are (6.1):

- OAB: urinary tract infection, dysuria, urinary retention
- Adult Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Pediatric Detrusor Overactivity associated with a neurologic condition: urinary tract infection, leukocyturia, bacteriuria
- Chronic Migraine: neck pain, headache
- Adult Spasticity: pain in extremity
- 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

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Patients receiving concomitant treatment of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX may be potentiated (7.1, 7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Adult Bladder Dysfunction

Overactive Bladder

BOTOX for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

1.2 Pediatric Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the 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.

1.3 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Limitations of Use

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

1.4 Spasticity

BOTOX is indicated for the treatment of spasticity in patients 2 years of age and older.

Limitations of Use

BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture.

1.5 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.6 Primary Axillary Hyperhidrosis

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Limitations of Use

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.7 Blepharospasm and Strabismus

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection 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 BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Warnings and Precautions (5.2) and Description (11)]*.

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3-month interval. In pediatric patients, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval *[see Dosage and Administration (2.7)]*.

The safe and effective use of BOTOX depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. An understanding of standard electromyographic techniques is also required for treatment of strabismus, upper or lower limb spasticity, and may be useful for the treatment of cervical dystonia. Physicians administering BOTOX must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

Do not use BOTOX and contact Allergan (1-800-890-4345) if:

- the carton labeling does not contain an intact seal with a translucent silver Allergan logo (on both ends of the carton) or the seal has a black circle with a diagonal line through it (i.e., prohibition sign),
- the vial label does not contain a holographic film containing the name “Allergan” within rainbow colored horizontal lines, or
- the U.S. License number 1145 is not present on the vial label and carton labeling *[see How Supplied/Storage and Handling (16)]*.

2.2 Preparation and Dilution Technique

Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection, USP. Draw up the proper amount of diluent in the appropriate size syringe (see Table 1, or for specific instructions for detrusor overactivity associated with a neurologic condition, see Section 2.3), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the diluent by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 24 hours after reconstitution. During this time period, unused reconstituted BOTOX should be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use. BOTOX vials are for single-dose only. Discard any unused portion.

Table 1: Dilution Instructions for BOTOX Vials (50 units, 100 Units and 200 Units)**

Diluent* Added to 50 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 200 Unit Vial	Resulting Dose Units per 0.1 mL
1 mL	5 Units	1 mL	10 Units	1 mL	20 Units
2 mL	2.5 Units	2 mL	5 Units	2 mL	10 Units
4 mL	1.25 Units	4 mL	2.5 Units	4 mL	5 Units
		8 mL	1.25 Units	8 mL	2.5 Units
		10 mL	1 Unit	10 mL	2 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

**For Detrusor Overactivity associated with a Neurologic Condition Dilution, see Section 2.3

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

An injection of BOTOX is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile needle and syringe should be used to enter the vial on each occasion for removal of BOTOX.

Reconstituted BOTOX should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

2.3 Adult Bladder Dysfunction

General

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics, except aminoglycosides, *[see Drug Interactions (7.1)]* should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Dispose of any unused saline.

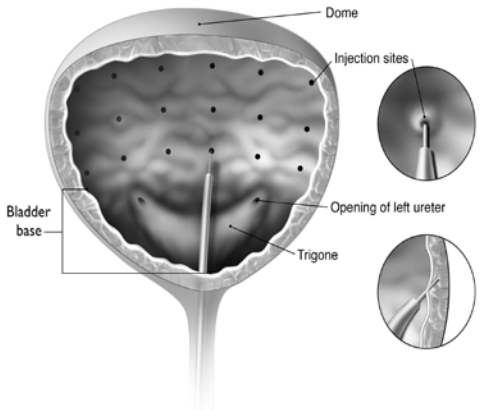
Reconstituted BOTOX (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, patients should demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median time until patients qualified for the second treatment of BOTOX in double-blind, placebo-controlled clinical studies was 169 days [~24 weeks]), but no sooner than 12 weeks from the prior bladder injection.

Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity Associated with a Neurologic Condition



Detrusor Overactivity associated with a Neurologic Condition
An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 Units of BOTOX per treatment, and should not be exceeded.

200 Unit Vial of BOTOX
- Reconstitute a 200 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 8 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

100 Unit Vial of BOTOX
- Reconstitute two 100 Unit vials of BOTOX, each with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vials gently.
- Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe for a total of 4 mL in each syringe.
- Complete the reconstitution by adding 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, placebo-controlled clinical studies was 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.4 Pediatric Detrusor Overactivity associated with a Neurologic Condition

Patients must not have a urinary tract infection (UTI) at the time of treatment. Oral prophylactic antibiotics, except aminoglycosides, *[see Drug Interactions (7.1)]* should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI. Alternatively, for patients receiving general anesthesia (or conscious sedation) for the treatment of detrusor overactivity associated with a neurologic condition, one dose of IV prophylactic antibiotics, except aminoglycosides, *[see Drug Interactions (7.1)]* may be administered prior to treatment administration on the day of treatment.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

- In patients 5 years to less than 12 years of age: Consider general anesthesia (or conscious sedation) prior to injection, per local site practice.
- In patients 12 years of age or older: Consider an intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia prior to injection, per local site practice.

At a minimum, consider a diluted instillation of local anesthetic for all age groups. If a local anesthetic instillation is performed, drain and irrigate the bladder with sterile saline before injection.

If patient's body weight is greater than or equal to 34 kg, the recommended dosage is 200 Units of BOTOX per treatment administered as an intradetrusor injection after dilution:

- Reconstitute BOTOX to result in 20 Units BOTOX/mL in the vial(s):
  - BOTOX 200 Unit vial: add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
  - BOTOX 100 Unit vials: add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to each of two 100 Unit vials of BOTOX and mix the vials gently.
- Draw 10 mL from the vial(s) into one 10 mL dosing syringe.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

If patient's body weight is less than 34 kg, the recommended dosage is 6 Units/kg body weight administered as a bladder injection after dilution (refer to Table 2):

- Reconstitute BOTOX to result in 20 Units BOTOX/mL in the vial(s):
  - BOTOX 200 Unit vial: add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
  - BOTOX 100 Unit vial(s): add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to one 100 Unit vial of BOTOX (if final dose is less than or equal to100 U) or to each of two 100 Unit vials of BOTOX (if final dose is greater than 100 U) and mix the vial(s) gently.
- Refer to Table 2 for dilution instructions (i.e., the amount of reconstituted BOTOX and additional diluent to draw into one 10 mL dosing syringe).
- Use BOTOX immediately after reconstitution in the syringe. Dispose of any unused preservative-free 0.9% Sodium Chloride Injection, USP.

Table 2: BOTOX Dilution Instructions and Final Dosing for Patients with Body Weight < 34 kg

Body Weight (kg)	Volume of reconstituted BOTOX and Diluent* (mL) to draw into dosing syringe to achieve a final volume of 10 mL		Final dose of BOTOX in dosing syringe
	BOTOX (mL)	Diluent* (mL)	
12 to less than 14	3.6	6.4	72 Units
14 to less than 16	4.2	5.8	84 Units
16 to less than 18	4.8	5.2	96 Units
18 to less than 20	5.4	4.6	108 Units
20 to less than 22	6	4	120 Units
22 to less than 24	6.6	3.4	132 Units
24 to less than 26	7.2	2.8	144 Units
26 to less than 28	7.8	2.2	156 Units
28 to less than 30	8.4	1.6	168 Units
30 to less than 32	9	1	180 Units
32 to less than 34	9.6	0.4	192 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

Reconstituted BOTOX is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, parallel group clinical study was 207 days [30 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.5 Chronic Migraine

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL (see Table 1). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams and Table 3 below. A one inch needle may be needed in the neck region for patients with thick neck muscles. With the exception of the procerus muscle, which should be injected at one site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks.

Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine

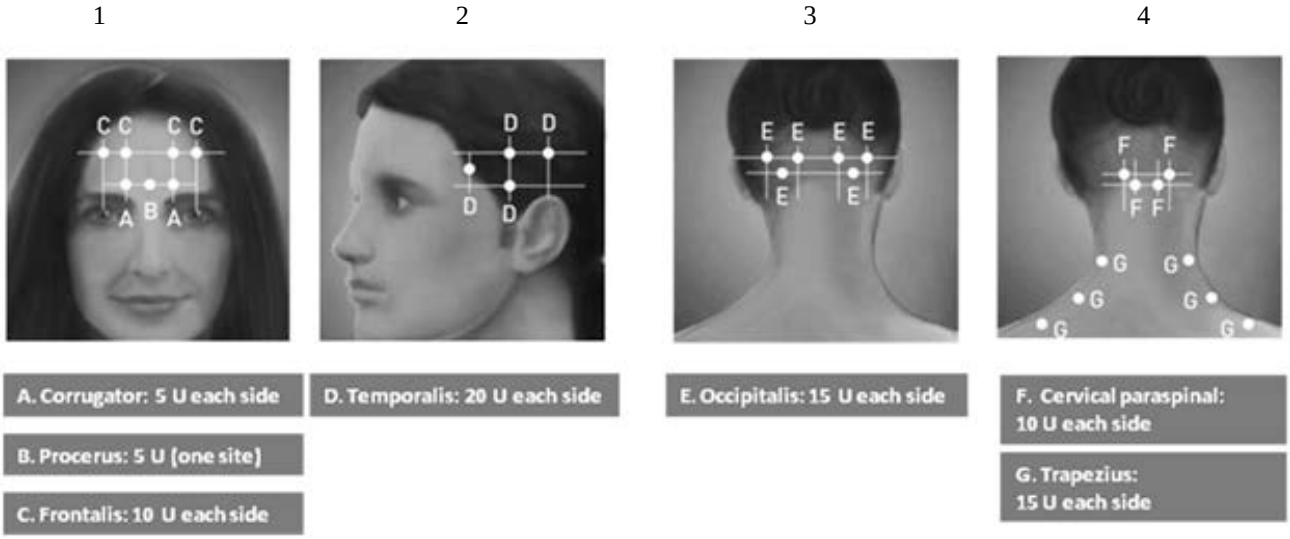


Table 3: BOTOX Dosing by Muscle for Chronic Migraine

Head/Neck Area	Recommended Dose (Number of Sites[a])
Frontalis[b]	20 Units divided in 4 sites
Corrugator[b]	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis[b]	30 Units divided in 6 sites
Temporalis[b]	40 Units divided in 8 sites
Trapezius[b]	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group[b]	20 Units divided in 4 sites
Total Dose:	**155 Units** divided **in 31 sites**

[a] Each IM injection site = 0.1 mL = 5 Units BOTOX
[b] Dose distributed bilaterally

2.6 Adult Spasticity

General

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with BOTOX.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended.

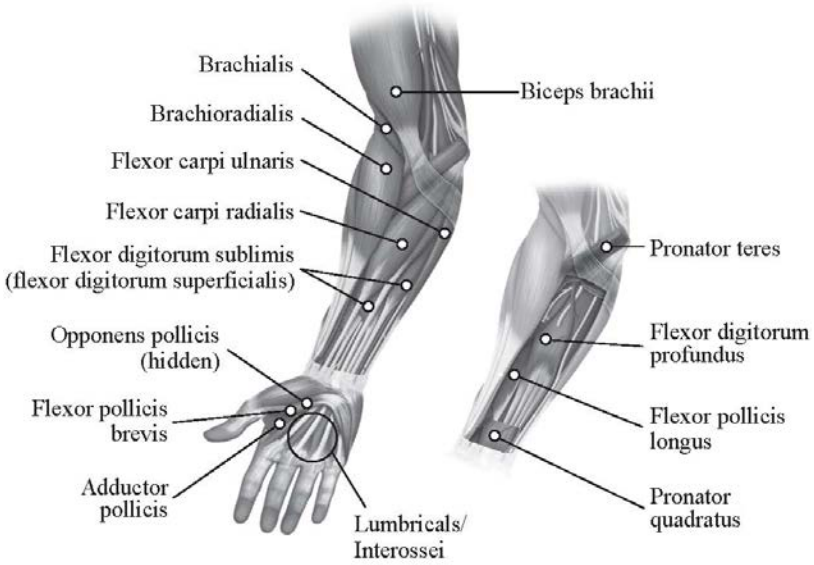
Repeat BOTOX treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected.

Adult Upper Limb Spasticity
In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 4 and Figure 2) at a given treatment session.

Table 4: BOTOX Dosing by Muscle for Adult Upper Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Biceps Brachii	60 Units to 200 Units divided in 2 to 4 sites
Brachioradialis	45 Units to 75 Units divided in 1 to 2 sites
Brachialis	30 Units to 50 Units divided in 1 to 2 sites
Pronator Teres	15 Units to 25 Units in 1 site
Pronator Quadratus	10 Units to 50 Units in 1 site
Flexor Carpi Radialis	12.5 Units to 50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units to 50 Units in 1 site
Flexor Digitorum Profundus	30 Units to 50 Units in 1 site
Flexor Digitorum Sublimis	30 Units to 50 Units in 1 site
Lumbricals/Interossei	5 Units to 10 Units in 1 site
Adductor Pollicis	20 Units in 1 site
Flexor Pollicis Longus	20 Units in 1 site
Flexor pollicis brevis/ Opponens pollicis	5 Units to 25 Units in 1 site

Figure 2: Injection Sites for Adult Upper Limb Spasticity



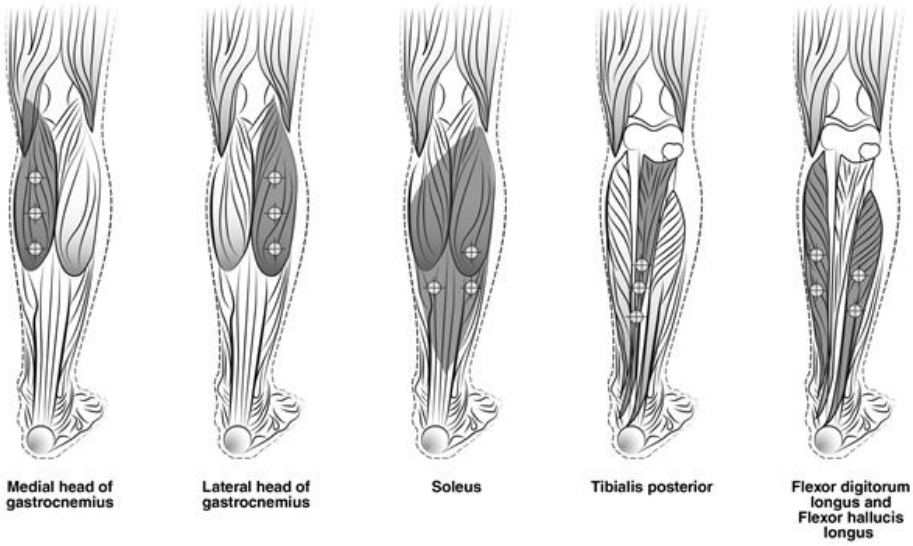
Adult Lower Limb Spasticity

The recommended dose for treating adult lower limb spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see Table 5 and Figure 3).

Table 5: BOTOX Dosing by Muscle for Adult Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	75 Units divided in 3 sites
Gastrocnemius lateral head	75 Units divided in 3 sites
Soleus	75 Units divided in 3 sites
Tibialis Posterior	75 Units divided in 3 sites
Flexor hallucis longus	50 Units divided in 2 sites
Flexor digitorum longus	50 Units divided in 2 sites

Figure 3: Injection Sites for Adult Lower Limb Spasticity



2.7 Pediatric Spasticity

General

Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended. When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval *[see Boxed Warning and Warnings and Precautions (5.1, 5.6)]*. Additional *general* adult spasticity dosing information is also applicable to pediatric spasticity patients *[see Dosage and Administration (2.6)]*.

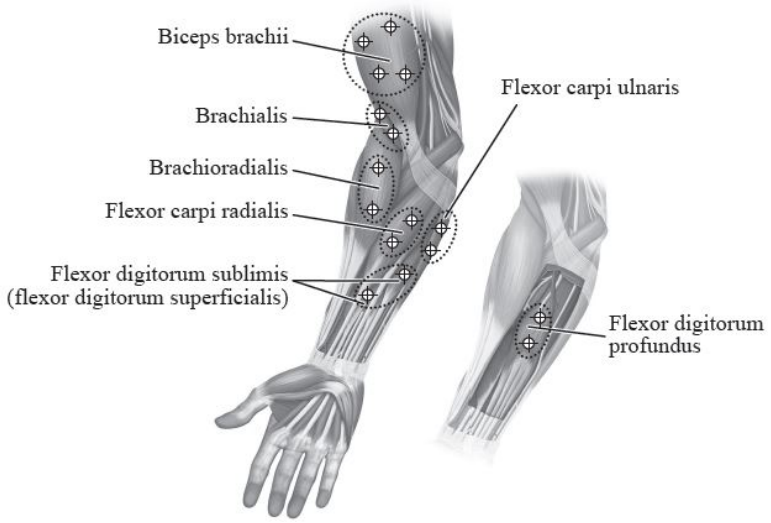
Pediatric Upper Limb Spasticity

The recommended dose for treating pediatric upper limb spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles (see Table 6 and Figure 4). The total dose of BOTOX administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower.

Table 6: BOTOX Dosing by Muscle for Pediatric Upper Limb Spasticity

Muscle	Recommended Dose and Number of Sites
Biceps Brachii	1.5 Units/kg to 3 Units/kg divided in 4 sites
Brachialis	1 Unit/kg to 2 Units/kg divided in 2 sites
Brachioradialis	0.5 Units/kg to 1 Unit/kg divided in 2 sites
Flexor Carpi Radialis	1 Unit/kg to 2 Units/kg divided in 2 sites
Flexor Carpi Ulnaris	1 Unit/kg to 2 Units/kg divided in 2 sites
Flexor Digitorum Profundus	0.5 Units/kg to 1 Unit/kg divided in 2 sites
Flexor Digitorum Sublimis	0.5 Units/kg to 1 Unit/kg divided in 2 sites

Figure 4: Injection Sites for Pediatric Upper Limb Spasticity



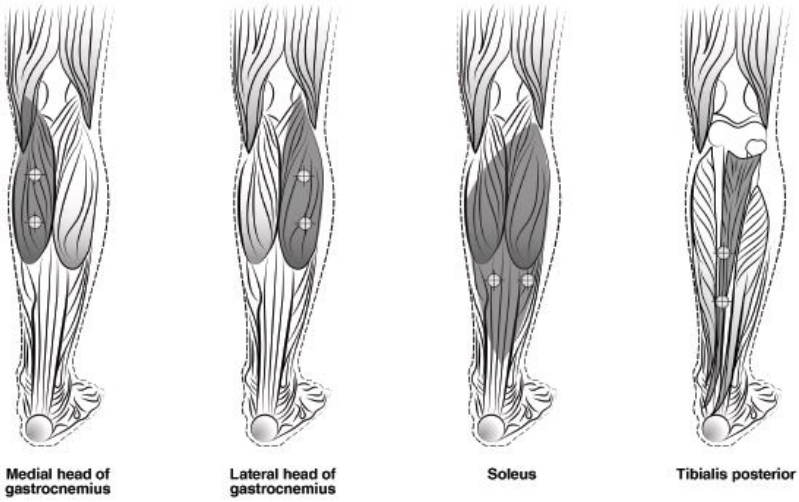
Pediatric Lower Limb Spasticity

The recommended dose for treating pediatric lower limb spasticity is 4 Units/kg to 8 Units/kg divided among the affected muscles (see Table 7 and Figure 5). The total dose of BOTOX administered per treatment session in the lower limb should not exceed 8 Units/kg or 300 Units, whichever is lower.

Table 7: BOTOX Dosing by Muscle for Pediatric Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	1 Unit/kg to 2 Units/kg divided in 2 sites
Gastrocnemius lateral head	1 Unit/kg to 2 Units/kg divided in 2 sites
Soleus	1 Unit/kg to 2 Units/kg divided in 2 sites
Tibialis Posterior	1 Unit/kg to 2 Units/kg divided in 2 sites

Figure 5: Injection Sites for Pediatric Lower Limb Spasticity



2.8 Cervical Dystonia

A double-blind, placebo-controlled study enrolled patients who had extended histories of receiving and tolerating BOTOX injections, with prior individualized adjustment of dose. The mean BOTOX dose administered to patients in this study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The BOTOX dose was divided among the affected muscles *[see Clinical Studies (14.7)]*.

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of BOTOX should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia *[see Warnings and Precautions (5.1, 5.5, 5.6)]*.

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 1). In general, no more than 50 Units per site should be administered using a sterile needle (e.g., 25-30 gauge) of an appropriate length. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the double-blind, placebo-controlled study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.9 Primary Axillary Hyperhidrosis

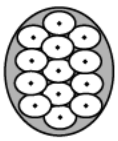
The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Using a sterile 30 gauge needle, 50 Units of BOTOX (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine-Starch Test Procedure:
Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise or hot drinks for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 6.

Figure 6: Injection Pattern for Primary Axillary Hyperhidrosis



Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject BOTOX directly through the ink mark to avoid a permanent tattoo effect.

2.10 Blepharospasm

For blepharospasm, reconstituted BOTOX is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units-2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Table 1).

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient, usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Some tolerance may be found when BOTOX is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of BOTOX treatment for blepharospasm in a 30-day period should not exceed 200 Units.

2.11 Strabismus

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

The volume of BOTOX injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX *[see Dosage and Administration (2.2)]* typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

Initial Doses in Units

Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

Subsequent Doses for Residual or Recurrent Strabismus

- It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Table 1).

3 DOSAGE FORMS AND STRENGTHS

For Injection: sterile 50 Units, sterile 100 Units or 200 Units vacuum-dried powder in single-dose vials for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection, USP prior to injection.

4 CONTRAINDICATIONS

BOTOX is contraindicated:

- In patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation *[see Warnings and Precautions (5.4)]*.
- In the presence of infection at the proposed injection site(s).
- For intradetrusor injection in patients with a urinary tract infection; or in patients with urinary retention or post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC) *[see Warnings and Precautions (5.12, 5.13)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Toxin Effect

Postmarketing safety data from BOTOX 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, 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, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for blepharospasm at the recommended dose (30 Units and below), severe primary axillary hyperhidrosis at the recommended dose (100 Units), strabismus, or for chronic migraine at the labeled doses have been reported.

5.2 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX 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 BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

5.5 Increased Risk of Clinically Significant Effects with 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 when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX *[see Warnings and Precautions (5.1, 5.6)]*.

5.6 Dysphagia and Breathing Difficulties

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing 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 oropharyngeal muscles that control swallowing or breathing *[see Warnings and Precautions (5.1)]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, 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 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 postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

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 Warnings and Precautions (5.1)]*.

5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated with a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in adult patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV_1 40-80% of predicted value and $FEV_1/FVC \leq 0.75$), the event rate in change of Forced Vital Capacity (FVC) ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 8).

Table 8: Event Rate Per Patient Treatment Cycle Among Adult Upper Limb Spasticity Patients with Reduced Lung Function Who Experienced at Least a 15% or 20% Decrease in FVC From Baseline at Week 1, 6, 12 Post-injection with Up to Two Treatment Cycles with BOTOX or Placebo

	BOTOX 360 Units		BOTOX 240 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In adult spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo *[see Warnings and Precautions (5.10)]*.

In a double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 9).

Table 9: Number and Percent of Patients Experiencing at Least a 15% or 20% Decrease in FVC From Baseline at Week 2, 6, 12 Post-Injection with BOTOX or Placebo

	BOTOX 200 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%
Week 2	0/15 (0%)	0/15 (0%)	1/11 (9%)	0/11 (0%)
Week 6	2/13 (15%)	1/13 (8%)	0/12 (0%)	0/12 (0%)
Week 12	0/12(0%)	0/12 (0%)	0/7 (0%)	0/7 (0%)

5.8 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

Reduced blinking from BOTOX injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated with a Neurologic Condition

Autonomic dysreflexia associated with intradetrusor injections of BOTOX could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in adult patients treated with BOTOX 200 Units compared with placebo (1.5% versus 0.4%, respectively).

5.12 Urinary Tract Infections in Patients with Overactive Bladder

BOTOX increases the incidence of urinary tract infection *[see Adverse Reactions (6.1)]*. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

5.13 Urinary Retention in Adults Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

The incidence and duration of urinary retention is described below for adult patients with overactive bladder and detrusor overactivity associated with a neurologic condition who received BOTOX or placebo injections.

Overactive Bladder

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with BOTOX or placebo is shown in Table 10. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 10: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB

Timepoint	BOTOX 100 Units (N=552)	Placebo (N=542)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
Duration of Catheterization for Urinary Retention (Days)		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 11.

Table 11: Proportion of Patients Experiencing Urinary Retention Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Adult Detrusor Overactivity associated with a Neurologic Condition
In two double-blind, placebo-controlled trials in adult patients with detrusor overactivity associated with a neurologic condition (NDO-1 and NDO-2), the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX 200 Units or placebo is shown in Table 12. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 12: Proportion of Adult Patients Not Using CIC at Baseline and then Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials

Timepoint	BOTOX 200 Units (N=108)	Placebo (N=104)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	30.6% (n=33)	6.7% (n=7)
Duration of Catheterization for Urinary Retention (Days)		
Median	289	358
Min, Max	1, 530	2, 379

Among adult patients not using CIC at baseline, those with Multiple Sclerosis (MS) were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 13).

Table 13: Proportion of Adult Patients by Etiology (MS and SCI) Not Using CIC at Baseline and then Catheterizing for Urinary Retention Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials

Timepoint	MS		SCI	
	BOTOX 200 Units (N=86)	Placebo (N=88)	BOTOX 200 Units (N=22)	Placebo (N=16)
At any time during complete treatment cycle	31% (n=27)	5% (n=4)	27% (n=6)	19% (n=3)

A placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) was conducted in non-catheterizing adult MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. Catheterization for urinary retention was initiated in 15.2% (10/66) of patients following treatment with BOTOX 100 Units versus 2.6% (2/78) on placebo at any time during the complete treatment cycle. The median duration of post-injection catheterization for those who developed urinary retention was 64 days for BOTOX 100 Units and 2 days for placebo.

5.14 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.

6 ADVERSE REACTIONS

The following adverse reactions to BOTOX (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.1)]*
- Serious Adverse Reactions with Unapproved Use *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Contraindications (4) and Warnings and Precautions (5.4)]*

- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders *[see Warnings and Precautions (5.5)]*
- Dysphagia and Breathing Difficulties *[see Warnings and Precautions (5.6)]*
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated with a Neurologic Condition *[see Warnings and Precautions (5.7)]*
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm *[see Warnings and Precautions (5.8)]*
- Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus *[see Warnings and Precautions (5.9)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.10)]*
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated with a Neurologic Condition *[see Warnings and Precautions (5.11)]*
- Urinary Tract Infections in Patients with Overactive Bladder *[see Warnings and Precautions (5.12)]*
- Urinary Retention in Patients Treated for Bladder Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse reactions observed with the use of BOTOX Cosmetic also have the potential to be observed with the use of BOTOX.

In general, adverse reactions occur within the first week following injection of BOTOX and, while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (including syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.1)]*.

Overactive Bladder

Table 14 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 14: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Often than in Placebo-Treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-Blind, Placebo-Controlled Clinical Trials in Patients with OAB

Adverse Reactions	BOTOX 100 Units (N=552) %	Placebo (N=542) %
Urinary tract infection	18	6
Dysuria	9	7
Urinary retention	6	0
Bacteriuria	4	2
Residual urine volume*	3	0

*Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥350 mL regardless of symptoms, and for PVR ≥200 mL to <350 mL with symptoms (e.g., voiding difficulty).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 15.

Table 15: Proportion of Patients Experiencing Urinary Tract Infection Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81) %	Placebo (N=69) %	BOTOX 100 Units (N=526) %	Placebo (N=516) %
Urinary tract infection (UTI)	31	12	26	10

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

Adult Detrusor Overactivity associated with a Neurologic Condition
Table 16 presents the most frequently reported adverse reactions in the double-blind, placebo-controlled studies within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX 200 Units.

Table 16: Adverse Reactions Reported by ≥2% of BOTOX-Treated Patients and More Frequent than in Placebo-Treated Patients Within the First 12 Weeks after Intradetrusor Injection in Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	BOTOX 200 Units (N=262) %	Placebo (N=272) %
Urinary tract infection	24	17
Urinary retention	17	3
Hematuria	4	3

The following adverse reactions with BOTOX 200 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 44 weeks): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

In the Multiple Sclerosis (MS) patients enrolled in the double-blind, placebo-controlled trials, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX and 0.20 for placebo.

No change was observed in the overall safety profile with repeat dosing.

Table 17 presents the most frequently reported adverse reactions in a placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) conducted in MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and not catheterized at baseline. The table below presents the most frequently reported adverse reactions within 12 weeks of injection.

Table 17: Adverse Reactions Reported in a Post Approval Study (NDO-3) by >2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients Within the First 12 Weeks after Intradetrusor Injection

Adverse Reactions	BOTOX 100 Units (N=66) %	Placebo (N=78) %
Urinary tract infection	26	6
Bacteriuria	9	5
Urinary retention	15	1
Dysuria	5	1
Residual urine volume*	17	1

* Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥350 mL regardless of symptoms, and for PVR ≥200 mL to <350 mL with symptoms (e.g., voiding difficulty).

The following adverse events with BOTOX 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 51 weeks): urinary tract infections (39%), bacteriuria (18%), urinary retention (17%),

residual urine volume* (17%), dysuria (9%), and hematuria (5%).

No difference in the MS exacerbation annualized rate (i.e., number of MS exacerbating events per patient-year) was observed (BOTOX =0, placebo =0.07).

Pediatric Detrusor Overactivity associated with a Neurologic Condition
Table 18 presents the most frequently reported adverse reactions in Study 191622-120, a double-blind, parallel-group study conducted in pediatric patients with detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and were using clean intermittent catheterization at baseline *[see Clinical Studies (14.3)]*. The table below presents the most frequently reported adverse reactions during the 12 weeks following intradetrusor administration of BOTOX 200 Units.

Table 18: Adverse Reactions Reported by ≥ 3% of BOTOX Treated Pediatric Patients within the First 12 Weeks after Intradetrusor Injection, Study 191622-120

Adverse Reactions	**BOTOX 200 Unit (N=30)**
Urinary tract infection	2 (7%)
Bacteriuria	6 (20%)
Leukocyturia	2 (7%)
Hematuria	1 (3%)

No change was observed in the overall safety profile with repeat dosing.

The most common adverse reactions in patients who received BOTOX 6 U/kg and less than a total dose of 200 U in Study 191622-120 were urinary tract infection (UTI), bacteriuria and hematuria.

Chronic Migraine
In double-blind, placebo-controlled chronic migraine efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the BOTOX treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the BOTOX group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the BOTOX group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 19.

Table 19: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients in Two Chronic Migraine Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	BOTOX 155 Units-195 Units (N=687) %	Placebo (N=692) %
Nervous system disorders		
Headache	5	3
Migraine	4	3
Facial paresis	2	0
Eye disorders		
Eyelid ptosis	4	<1
Infections and Infestations		
Bronchitis	3	2
Musculoskeletal and connective tissue disorders		
Neck pain	9	3
Musculoskeletal stiffness	4	1
Muscular weakness	4	<1
Myalgia	3	1
Musculoskeletal pain	3	1
Muscle spasms	2	1
General disorders and administration site conditions		
Injection site pain	3	2
Vascular Disorders		
Hypertension	2	1

Other adverse reactions that occurred more frequently in the BOTOX group compared to the placebo group at a frequency less than 1% and potentially BOTOX related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Adult Upper Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 20.

Table 20: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients in Adult Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	BOTOX 251 Units - 360 Units (N=115) %	BOTOX 150 Units - 250 Units (N=188) %	BOTOX <150 Units (N=54) %	Placebo (N=182) %
Gastrointestinal disorder				
Nausea	3	2	2	1
General disorders and administration site conditions				
Fatigue	3	2	2	0
Infections and infestations				
Bronchitis	3	2	0	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	6	5	9	4
Muscular weakness	0	4	2	1

Twenty-two adult patients, enrolled in double-blind placebo controlled studies, received 400 Units or higher of BOTOX for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX or higher for four consecutive treatments over approximately one year for treatment of upper limb spasticity. The type and frequency of adverse reactions observed in patients treated with 400 Units of BOTOX were similar to those reported in patients treated for upper limb spasticity with 360 Units of BOTOX.

Adult Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 21. Two hundred thirty-one patients enrolled in a double-blind placebo controlled study (Study 8) received 300 Units to 400 Units of BOTOX, and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

Table 21: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients in Adult Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 8)

Adverse Reactions	BOTOX (N=231) %	Placebo (N=233) %
Musculoskeletal and connective tissue disorders		
Arthralgia	3	1
Back pain	3	2
Myalgia	2	1
Infections and infestations		
Upper respiratory tract infection	2	1
General disorders and administration site conditions		
Injection site pain	2	1

Pediatric Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric patients 2 to 17 years of age with upper limb spasticity appear in Table 22. In a double-blind, placebo-controlled trial (Study 1), 78 patients were treated with 3 Units/kg of BOTOX, and 77 patients received 6 Units/kg to a maximum dose of 200 Units of BOTOX, and were compared to 79 patients who received placebo *[see Clinical Studies (14.5)]*. Patients were followed for an average of 91 days after injection.

Table 22: Adverse Reactions Reported by ≥2% of BOTOX 6 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 1)

Adverse Reactions	BOTOX 6 Units/kg (N=77) %	BOTOX 3 Units/kg (N=78) %	Placebo (N=79) %
Infections and infestations			
Upper respiratory tract infection*	17	10	9
General disorders and administration site conditions			
Injection site pain	4	3	1
Gastrointestinal disorders			
Nausea	4	0	0
Constipation	3	0	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	4	0	1
Nasal congestion	3	0	1
Nervous system disorders			
Seizure**	5	1	0

*Includes upper respiratory tract infection and viral upper respiratory tract infection

**Includes seizure and partial seizure

Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric patients 2 to 17 years of age with lower limb spasticity appear in Table 23. In a double-blind, placebo-controlled trial (Study 2), 126 patients were treated with 4 Units/kg of BOTOX, and 128 patients received 8 Units/kg to a maximum dose of 300 Units of BOTOX, and were compared to 128 patients who received placebo *[see Clinical Studies (14.6)]*. Patients were followed for an average of 89 days after injection.

Table 23: Adverse Reactions Reported by ≥2% of BOTOX 8 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 2)

Adverse Reactions	BOTOX 8 Units/kg (N=128) %	BOTOX 4 Units/kg (N=126) %	Placebo (N=128) %
General disorders and administration site conditions			
Injection site erythema	2	0	0
Injection site pain	2	2	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	0	1
Injury, poisoning and procedural complications			
Ligament sprain	2	1	0
Skin abrasion	2	0	0
Metabolism and nutrition disorders			
Decreased appetite	2	0	0

Cervical Dystonia
In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles *[see Warnings and Precautions (5.1, 5.6)]*.

The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea *[see Warnings and Precautions (5.1, 5.6)]*. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms *[see Warnings and Precautions (5.6)]*.

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of BOTOX for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis
The most frequently reported adverse reactions (3-10% of adult patients) following injection of BOTOX in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to BOTOX 50 Units and 110 patients exposed to BOTOX 75 Units in each axilla.

Blepharospasm
In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured BOTOX, the most frequently reported adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from BOTOX injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus

Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%.

The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to onabotulinumtoxinA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to BOTOX therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to BOTOX therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), and no patients among 406 migraine patients with analyzed specimens developed the presence of neutralizing antibodies.

In one Phase 3 study and the open-label extension study in patients with pediatric lower limb spasticity, neutralizing antibodies developed in 2 of 264 patients (0.8%) treated with BOTOX for up to 5 treatment cycles. Both patients continued to experience clinical benefit following subsequent BOTOX treatments.

In overactive bladder patients with analyzed specimens from the two phase 3 studies and the open-label extension study, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. Response to subsequent BOTOX treatment was not different following seroconversion in these three patients.

In detrusor overactivity associated with neurologic condition patients with analyzable specimens in the adult drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to BOTOX in the remaining 2 patients is not known. In 99 pediatric patients who had a negative baseline result for binding antibodies or neutralizing antibodies and had at least one evaluable post-baseline value from one randomized double-blind study and one double-blind extension study, no patients developed neutralizing antibodies after receiving 50 Units to 200 Units of BOTOX.

The data reflect the patients whose test results were considered positive for neutralizing activity to BOTOX in a mouse protection assay or negative based on a screening ELISA assay or mouse protection assay.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; dry eye; eyelid edema (following periocular injection); hyperhidrosis; hypoacusis; hypoaesthesia; localized muscle twitching; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.4, 5.6)]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

7.2 Anticholinergic Drugs

Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects.

7.3 Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

7.4 Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX in pregnant women. In animal studies, administration of BOTOX during pregnancy resulted in adverse effects on fetal growth (decreased fetal weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated populations is unknown.

Data

Animal Data

When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

When BOTOX was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the human dose of 400 Units, based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 2 times the human dose of 400 Units, based on Units/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of BOTOX in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BOTOX and any potential adverse effects on the breastfed infant from BOTOX or from the underlying maternal conditions.

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) *[see Clinical Studies (14.3)]*. The most common adverse reactions in this population were urinary tract infection, bacteriuria, hematuria, and leukocyturia *[see Adverse Reactions (6.1)]*.

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 *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Studies (14.6)]*. 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 *[see Boxed Warning and Warnings and Precautions (5.1)]*.

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.

8.5 Geriatric Use

Of the 2145 adult patients in placebo-controlled clinical studies of BOTOX for the treatment of spasticity, 33.5% were 65 or older, and 7.7% were 75 years of age or older. No overall differences in safety were observed between elderly patients and adult patients younger than 65 years of age.

In clinical studies of BOTOX across other indications, no overall differences in safety were observed between elderly patients and younger adult patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified

differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

Overactive Bladder
Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% were 65 years of age or older, and 14.7% were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 24). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to adult patients younger than 65 years of age in these studies.

Table 24: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-Controlled Treatment, Placebo-Controlled Clinical Trials in Patients with OAB

	<65 Years		65 to 74 Years		≥75 Years	
Adverse Reactions	**BOTOX 100 Units (N=344) %**	**Placebo (N=348) %**	**BOTOX 100 Units (N=169) %**	**Placebo (N=151) %**	**BOTOX 100 Units (N=94) %**	**Placebo (N=86) %**
Urinary tract infection	21	7	30	13	38	19
Urinary retention	6	0.6	8	0	9	1

Observed effectiveness was comparable between these age groups in placebo-controlled clinical studies.

10 OVERDOSAGE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection *[see Boxed Warning and Warnings and Precautions (5.1, 5.6)]*. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

11 DESCRIPTION

OnabotulinumtoxinA is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A, and intended for intramuscular, intradetrusor and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of BOTOX (onabotulinumtoxinA) for injection contains either 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride; 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride; or 200 Units of Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or autonomic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX.

When injected intradermally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect BOTOX in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX.

Mutagenesis

BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicology assays.

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males: 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

In a study to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 Units/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 Units/kg (~12X the highest human bladder dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 Units/kg (~33X the highest human bladder dose [200 Units], based on Units/kg).

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 Units of BOTOX or placebo) spaced approximately 1 cm apart into the detrusor muscle.

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Table 25 and Table 26, and Figure 7 and Figure 8.

Table 25: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

	BOTOX 100 Units (N=278)	Placebo (N=272)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean Baseline	5.5	5.1		
Mean Change[*] at Week 2	-2.6	-1.0	-1.6	
Mean Change[*] at Week 6	-2.8	-1.0	-1.8	
Mean Change[*] at Week 12[**]	-2.5	-0.9	-1.6 (-2.1, -1.2)	<0.001
Daily Frequency of Micturition Episodes[b]				
Mean Baseline	12.0	11.2		
Mean Change[†] at Week 12[**]	-1.9	-0.9	-1.0 (-1.5, -0.6)	<0.001
Volume Voided per Micturition[b] (mL)				
Mean Baseline	156	161		
Mean Change[†] at Week 12[**]	38	8	30 (17, 43)	<0.001

[*] Least squares (LS) mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

[**] Primary timepoint

[a] Primary variable

[b] Secondary variable

Table 26: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

	BOTOX 100 Units (N=275)	Placebo (N=269)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean Baseline	5.5	5.7		
Mean Change[*] at Week 2	-2.7	-1.1	-1.6	
Mean Change[*] at Week 6	-3.1	-1.3	-1.8	
Mean Change[*] at Week 12[**]	-3.0	-1.1	-1.9 (-2.5, -1.4)	<0.001
Daily Frequency of Micturition Episodes[b]				
Mean Baseline	12.0	11.8		
Mean Change[†] at Week 12[**]	-2.3	-0.6	-1.7 (-2.2, -1.3)	<0.001
Volume Voided per Micturition[b] (mL)				
Mean Baseline	144	153		
Mean Change[†] at Week 12[**]	40	10	31 (20, 41)	<0.001

[*] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

[**] Primary timepoint

[a] Primary variable

[b] Secondary variable

Figure 7: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes Following Intradetrusor Injection in Study OAB-1

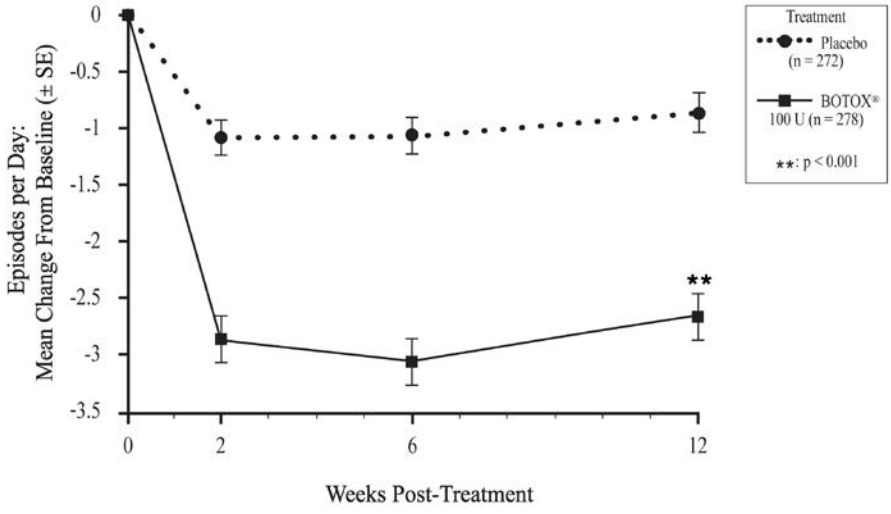
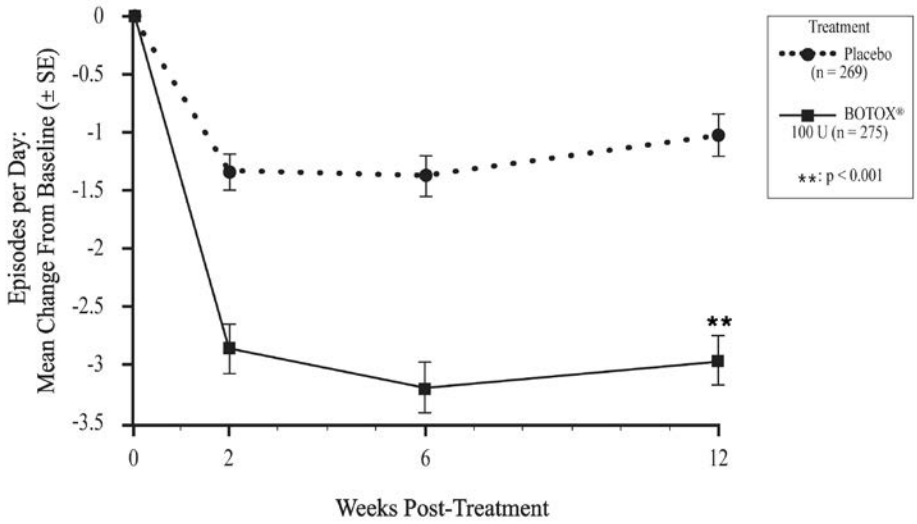


Figure 8: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes Following Intradetrusor Injection in Study OAB-2



The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19-24 weeks for the BOTOX 100 Unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days.

14.2 Adult Detrusor Overactivity Associated with a Neurologic Condition

Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 27 and Table 28, and Figure 9 and Figure 10.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

Table 27: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) Study NDO-1

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	134	146		
Mean Baseline	32.3	28.3		
Mean Change* at Week 2	-15.3	-10.0	-5.3	—
Mean Change* at Week 6**	-19.9	-10.6	-9.2 (-13.1, -5.3)	p<0.001
Mean Change* at Week 12	-19.8	-8.8	-11.0	—
Maximum Cystometric Capacity[b] (mL)				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change* at Week 6**	135.9	12.1	123.9 (89.1, 158.7)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change* at Week 6**	-28.1	-3.7	-24.4	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

** Primary timepoint

[a] Primary endpoint

[b] Secondary endpoint

Table 28: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-2

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	91	91		
Mean Baseline	32.7	36.8		
Mean Change* at Week 2	-18.0	-7.9	-10.1	—
Mean Change* at Week 6**	-19.6	-10.8	-8.8 (-14.5, -3.0)	p=0.003
Mean Change* at Week 12	-19.6	-10.7	-8.9	—
Maximum Cystometric Capacity[b] (mL)				
N	88	85		
Mean Baseline	239.6	253.8		
Mean Change* at Week 6**	150.8	2.8	148.0 (101.8, 194.2)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	29	68		
Mean Baseline	65.6	43.7		
Mean Change* at Week 6**	-28.7	2.1	-30.7	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

Figure 9: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-1

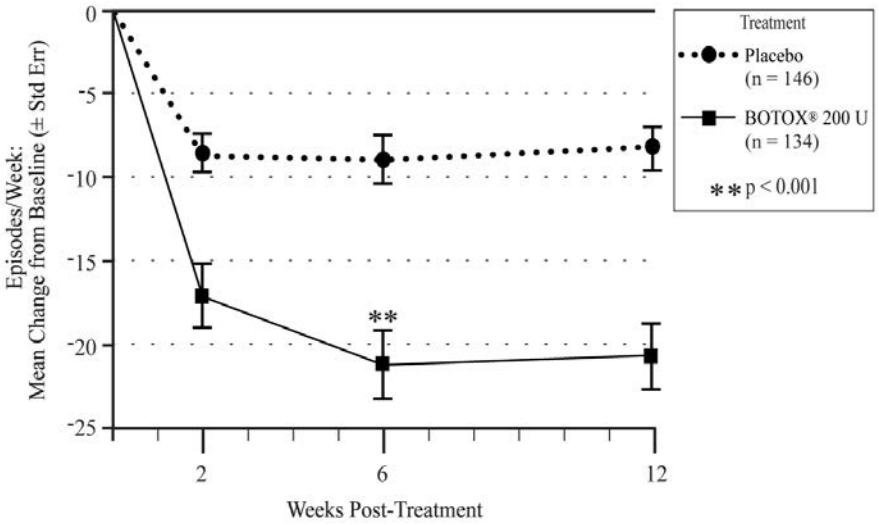
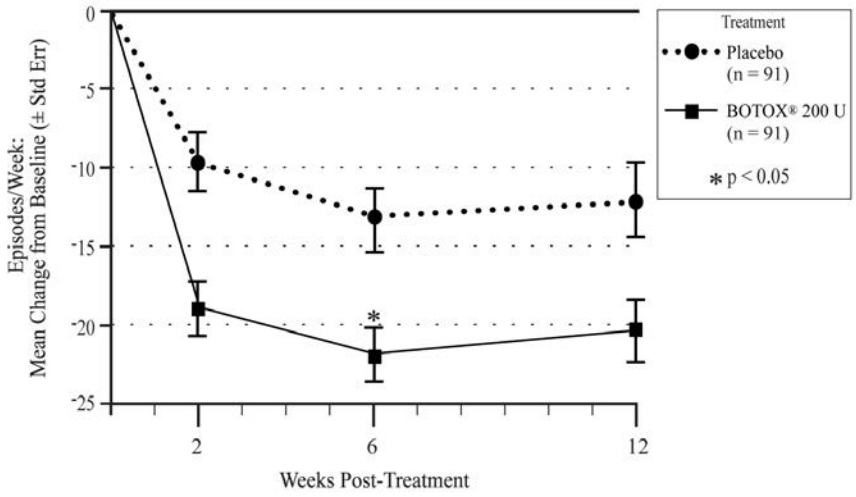


Figure 10: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2



The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

A placebo-controlled, double-blind randomized post-approval 52 week study (Study NDO-3) was conducted in MS patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either 100 Units of BOTOX (n=66) or placebo (n=78).

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX (100 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 29.

Table 29: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-3

	BOTOX 100 Units	Placebo	Treatment Difference*	p-value*
Daily Frequency of Urinary Incontinence Episodes[a]				
N	66	78		
Mean Baseline	4.2	4.3		
Mean Change* at Week 2	-2.9	-1.2	-1.7	—
Mean Change* at Week 6**	-3.4	-1.1	-2.3 (-3.0, -1.7)	p<0.001
Mean Change* at Week 12	-2.7	-1.0	-1.8	—
Maximum Cystometric Capacity[b] (mL)				
N	62	72		
Mean Baseline	248.9	245.5		
Mean Change* at Week 6**	134.4	3.5	130.9 (94.8, 167.0)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	25	51		
Mean Baseline	42.4	39.0		
Mean Change* at Week 6**	-19.2	2.7	-21.9 (-37.5, -6.3)	

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline daily endpoint as covariate and treatment group and propensity score stratification as factors. LOCF values were used to analyze the primary efficacy variable.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

The median duration of response in study NDO-3, based on patient qualification for re-treatment was 362 days (52 weeks) for the BOTOX 100 Units dose group compared to 88 days (13 weeks) for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days with no more than 1 incontinence-free day.

14.3 Pediatric Detrusor Overactivity Associated with a Neurologic Condition

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 and using clean intermittent catheterization. A total of 113 patients (including 99 with spinal dysraphism such as spina bifida, 13 with spinal cord injury and 1 with transverse myelitis) who had an inadequate response to or were intolerant of at least one anticholinergic medication were enrolled. The median age was 11 years (range: 5 to 17 years), 49% were female; 75% were White, 10% were Black. These patients were randomized to 50 Units, 100 Units or 200 Units, not to exceed 6 Units/kg body weight. Patients receiving less than the randomized dose due to the 6 Units/kg maximum, were assigned to the nearest dose group for analysis. The sample size for BOTOX 50 Units, 100 Units, and 200 Units were 38, 45 and 30, respectively. Prior to treatment administration, patients received anesthesia based on age and local site practice. One hundred and nine patients (97.3%) received general anesthesia or conscious sedation and 3 patients (2.7%) received local anesthesia.

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. Additional benefits were seen with BOTOX 200 Units for measures related to reducing maximum bladder pressure when compared to 50 Units. The decrease in maximum detrusor pressure (MDP) during the storage phase (MDP defined as the highest value in the Pdet channel during the storage phase [e.g., the greater of the following: the maximum Pdet during the highest amplitude IDC, the maximum Pdet during a terminal detrusor contraction, the Pdet at the end of filling, or the highest Pdet at any other time during the storage phase]) for BOTOX 200 Units at Week 6 was greater than the decrease observed for 50 Units. Within group improvements for the primary and secondary endpoints for the 200 Units dose group are shown in Table 30.

The efficacy of BOTOX 6 U/kg for pediatric patients with NDO weighing less than 34 kg was comparable to that of BOTOX 200 U.

Table 30: Baseline and Change from Baseline in Daily Daytime Frequency of Urinary Incontinence Episodes, Urine Volume at First Morning Catheterization, Maximum Detrusor Pressure during the Storage Phase (cmH_2O), and Maximum Cystometric Capacity (mL) in Study191622-120

	BOTOX 200 U N=30
Daily average frequency of daytime urinary incontinence episodes[a]	
Mean Baseline	3.7
Mean Change* at Week 2 (95% CI)	-1.1 (-1.7, -0.6)
Mean Change* at Week 6** (95% CI)	-1.3 (-1.8, -0.9)
Mean Change* at Week 12 (95% CI)	-0.9 (-1.5, -0.4)
Urine Volume at First Morning Catheterization (mL)[b]	
Mean Baseline	187.7
Mean Change* at Week 2 (95% CI)	63.2 (27.9, 98.6)
Mean Change* at Week 6** (95% CI)	87.5 (52.1, 122.8)
Mean Change* at Week 12 (95% CI)	45.2 (10.0, 80.5)
Maximum Detrusor Pressure (PdetMax) During the Storage Phase (cm H2O)[b]	
Mean Baseline	56.7
Mean Change* at Week 6** (95% CI)	-27.3 (-36.4, -18.2)
Maximum Cystometric Capacity (mL) (MCC)[b]	
Mean Baseline	202.3
Mean Change* at Week 6** (95% CI)	63.6 (29.0, 98.1)

CI = Confidence Interval
* LSmean change and 95% CI are based on an ANCOVA model with baseline value as covariate and treatment group, age (< 12 years or >= 12 years), baseline daytime urinary incontinence episodes (<= 6 or > 6) and anticholinergic therapy (yes/no) at baseline as factors.
** Primary timepoint
[a] Primary endpoint
[b] Secondary endpoint

The median duration of response in this study, based on patient qualification for re-treatment was 207 days (30 weeks) for BOTOX 200 Units dose group. To qualify for re-treatment, patients must have reported at least 2 urinary incontinence episodes over 2 days and at least 12 weeks have passed from the prior bladder injection.

14.4 Chronic Migraine

BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had $\geq$15 headache days lasting 4 hours or more, with $\geq$50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 31).

Table 31: Week 24 Key Efficacy Variables for Study 1 and Study 2

Efficacy per 28 days	Study 1		Study 2	
	BOTOX (N=341)	Placebo (N=338)	BOTOX (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache on headache days	-107*	-70	-134*	-95

* Significantly different from placebo ($p \leq 0.05$)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 11), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 12), compared to placebo-treated patients.

Figure 11: Mean Change from Baseline in Number of Headache Days for Study 1

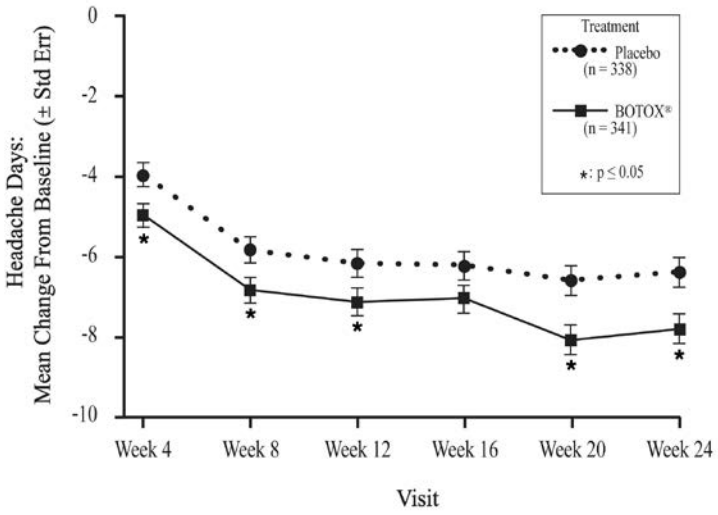
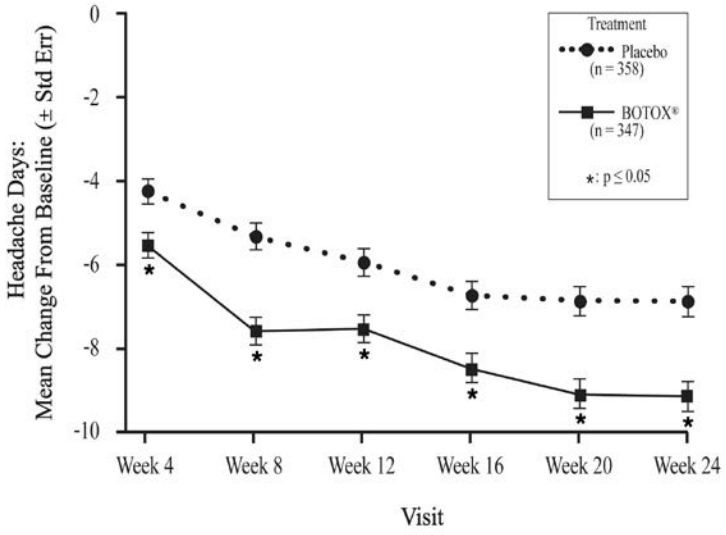


Figure 12: Mean Change from Baseline in Number of Headache Days for Study 2



14.5 Adult Spasticity

Adult Upper Limb Spasticity

The efficacy of BOTOX for the treatment of adult upper limb spasticity was evaluated in several randomized, multi-center, double-blind, placebo-controlled studies (Studies 1 through 6).

Study 1 included 126 adult patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 32). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 32: BOTOX Dose and Injection Sites in Study 1

Muscles Injected	Volume (mL)	BOTOX (Units)	Number of Injection Sites
Wrist Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
Finger Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
Thumb Adductor Pollicis[a]	0.4	20	1
Flexor Pollicis Longus[a]	0.4	20	1

[a] Injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 33.

Table 33: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

	BOTOX (N=64)	Placebo (N=62)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†a	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††b	-1.0*	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale††c	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment††	2.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] BOTOX injected into both the flexor carpi radialis and ulnaris muscles
[b] BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[c] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 adult patients [BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 34).

Table 34: BOTOX Dose and Injection Sites in Study 2 and Study 3

	Total Dose				
Muscles Injected	**BOTOX low dose (90 Units)**	**BOTOX mid dose (180 Units)**	**BOTOX high dose (360 Units)**	**Volume (mL) per site**	**Injection Sites (n)**
Wrist					
Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
Finger					
Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
Elbow					
Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 35.

Table 35: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

	BOTOX low dose (90 Units) (N=21)	**BOTOX mid dose (180 Units) (N=23)**	**BOTOX high dose (360 Units) (N=21)**	**Placebo (N=26)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†b	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††c	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††d	-0.5	-1.0*	-0.5[a]	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] p=0.053
[b] Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of BOTOX injected into biceps brachii muscle

Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 adult patients [BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 34).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 36.

Table 36: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

	BOTOX low dose (90 Units) (N=23)	BOTOX mid dose (180 Units) (N=21)	BOTOX high dose (360 Units) (N=22)	Placebo (N=19)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†b	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††c	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale†d	-0.5	-0.5	-1.0*	-0.5

† Primary endpoint at Week 4
†† Secondary endpoints at Week 4
* Significantly different from placebo ($p \leq 0.05$)
b Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles
c Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
d Dose of BOTOX injected into biceps brachii muscle

Study 4 (NCT01153815) included 170 adult patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units in thumb muscles) or placebo (see Table 37). Study 5 (NCT00460564) included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, adult patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus under EMG guidance (total BOTOX low dose = 30 Units, total BOTOX high dose = 40 Units), or placebo (see Table 37). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

Table 37: BOTOX Dose and Injection Sites in Studies 4 and 5

Muscles Injected	Study 4		Study 5				Number of Injection Sites for Studies 4 and 5
	BOTOX (Units)	Volume (mL)	BOTOX low dose (Units)	BOTOX high dose (Units)	Volume low dose (mL)	Volume high dose (mL)	
Thumb Adductor Pollicis	20	0.4	15	20	0.3	0.4	1
Flexor Pollicis Longus	20	0.4	15	20	0.3	0.4	1

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 38. The MAS uses a similar scoring system as the Ashworth Scale.

Table 38: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

	BOTOX (N=66)	Placebo (N=57)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale††a	-1.0*	0.0
Median Physician Global Assessment of Response to Treatment††	2.0*	0.0

†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.001$)
a BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function] are presented in Table 39.

Table 39: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

	BOTOX low dose (30 Units) (N=14)	Placebo low dose (N=9)	BOTOX high dose (40 Units) (N=43)	Placebo high dose (N=23)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale†††[a]	-1.0	-1.0	-0.5*	0.0
Median Change from Baseline in Clinical Global Impression Score by Physician ††	1.0	0.0	2.0*	0.0

†† Secondary endpoint at Week 6

††† Other endpoint at Week 6

* Significantly different from placebo ($p \leq 0.010$)

[a] BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 6 (NCT03261167) enrolled 124 post-stroke adult patients with upper limb spasticity. In Study 6, 61 patients received 160 Units BOTOX divided among 3 elbow flexors (biceps brachii, brachioradialis, and brachialis) and 63 patients received placebo (see Table 40). EMG, nerve stimulation, or ultrasound techniques were recommended to assist in proper muscle localization for injections. The duration of follow-up was 12 weeks.

Table 40: BOTOX Dose and Injection Sites in Study 6

Muscles Injected	BOTOX 160 U (Units)	Volume (mL)	Number of Injection Sites
Elbow Biceps Brachii	70	1.4	2
Brachioradialis	45	0.9	1
Brachialis	45	0.9	1

The change from baseline in elbow flexor tone measured by modified Ashworth Scale at Week 6 is presented in Table 41.

Table 41: Primary Efficacy Endpoint Results for Elbow Flexors at Week 6 in Study 6

	BOTOX 160 U (N=61)	Placebo (N=63)
Mean Change from Baseline in Elbow Flexor Muscle Tone on the modified Ashworth Scale at Week 6	-1.09*	-0.71

*nominal p value <0.05

Adult Lower Limb Spasticity

The efficacy and safety of BOTOX for the treatment of adult lower limb spasticity was evaluated in Study 7, a randomized, multi-center, double-blind, placebo-controlled study. Study 7 included 468 post-stroke adult patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 42) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

Table 42: BOTOX Dose and Injection Sites in Study 7

Muscles Injected	BOTOX (Units)	Number of Injection Sites
Mandatory Ankle Muscles Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
Optional Muscles Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement.

Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 43).

Table 43: Co-Primary Efficacy Endpoints Results in Study 7 (Intent-To-Treat Population)

	BOTOX 300 to 400 Units (N=233)	Placebo (N=235)
Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7

* Significantly different from placebo ($p<0.05$)

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 13) and CGI (see Figure 14) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

Figure 13: Modified Ashworth Scale Ankle Score for Study 7 – Mean Change from Baseline by Visit

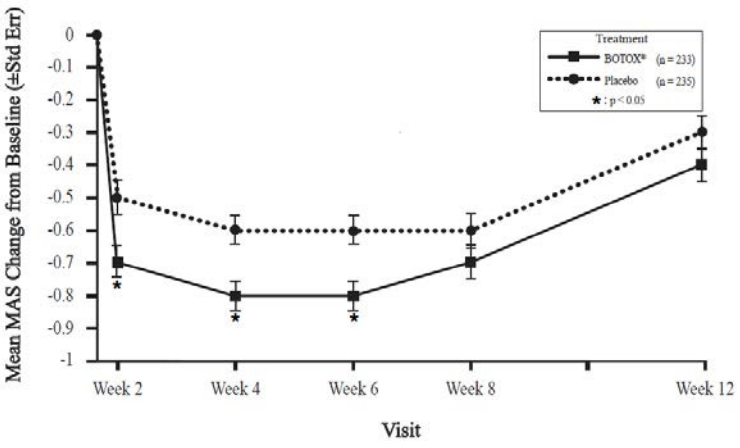
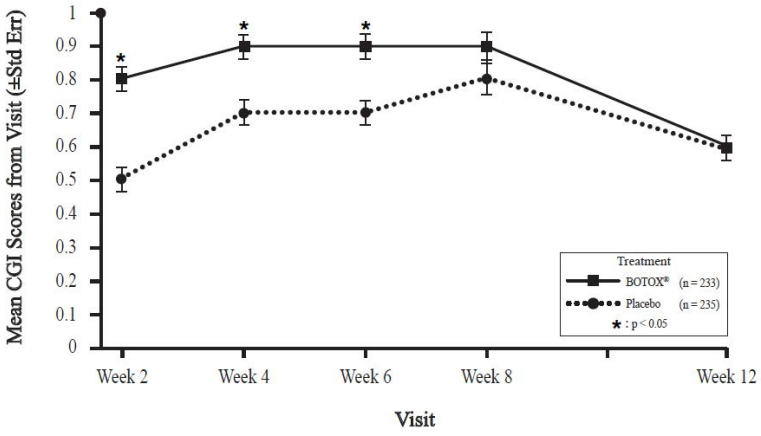


Figure 14: Clinical Global Impression by Physician for Study7 – Mean Scores by Visit



14.6 Pediatric Spasticity

Pediatric Upper Limb Spasticity

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 (78 BOTOX 3 Units/kg, 77 BOTOX 6 Units/kg, and 79 placebo) with upper limb spasticity (modified Ashworth Scale elbow or wrist score of at least 2) 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 (see Table 44). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

Table 44: BOTOX Dose and Injection Sites in Study 1

Muscles Injected	BOTOX 3 Units/kg* (maximum Units per muscle)	BOTOX 6 Units/kg** (maximum Units per muscle)	Number of Injection Sites
Elbow Flexor Muscles			
Biceps	1.5 Units/kg (50 Units)	3 Units/kg (100 Units)	4
Brachialis	1 Unit/kg (30 Units)	2 Units/kg (60 Units)	2
Brachioradialis	0.5 Units/kg (20 Units)	1 Unit/kg (40 Units)	2
Wrist and Finger Muscles			
Flexor carpi radialis	1 Unit/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor carpi ulnaris	1 Unit/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor digitorum profundus	0.5 Units/kg (25 Units)	1 Unit/kg (50 Units)	2
Flexor digitorum sublimis	0.5 Units/kg (25 Units)	1 Unit/kg (50 Units)	2

* Did not exceed a total dose of 100 Units

** Did not exceed a total dose of 200 Units

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) principal muscle group score (elbow or wrist) at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

Compared to placebo, significant improvements in MAS change from baseline were observed at all timepoints for BOTOX-treated patients (see Table 45, Figure 15 and Figure 16). Although CGI scores numerically favored BOTOX over placebo, the difference was not statistically significant.

Table 45: Co-Primary Efficacy Endpoints Results in Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population)

	BOTOX 3 Units/kg (N=78)	BOTOX 6 Units/kg (N=77)	Placebo (N=79)
Mean Change from Baseline in Principal Muscle Group (Elbow or Wrist) on the modified Ashworth Scale			
Week 4 and 6 Average	-1.92*	-1.87*	-1.21
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.88	1.87	1.66

*Nominal p value <0.05

Figure 15: Modified Ashworth Scale Score for Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) – Mean Change from Baseline by Visit

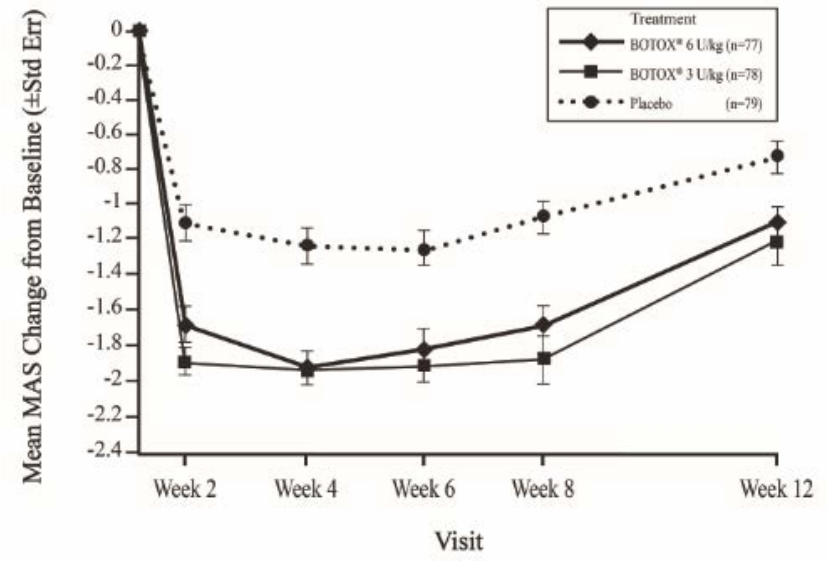
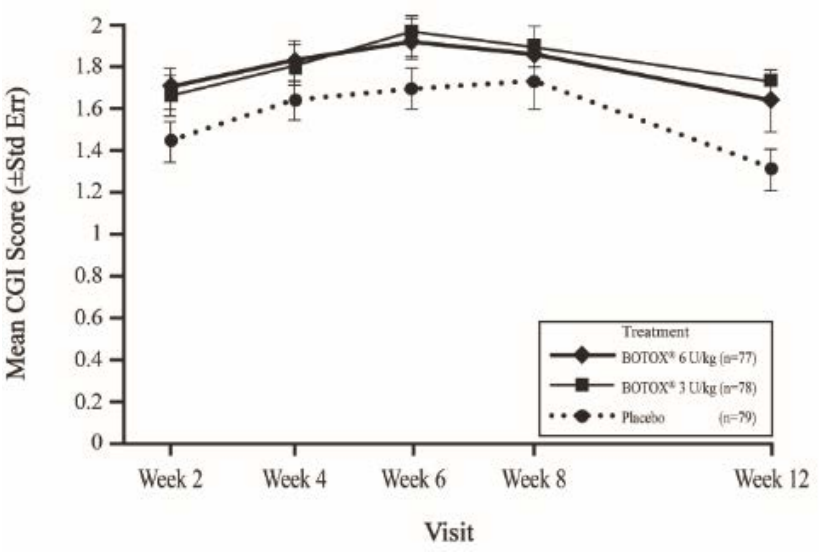


Figure 16: Clinical Global Impression of Overall Change for Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) – Mean Scores by Visit



Pediatric 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 (125 BOTOX 4 Units/kg, 127 BOTOX 8 Units/kg, and 129 placebo) with lower limb spasticity (modified Ashworth Scale ankle score of at least 2) 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 (see Table 46). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

Table 46: BOTOX Dose and Injection Sites in Study 2

Muscles Injected	BOTOX 4 Units/kg* (maximum Units per muscle)	BOTOX 8 Units/kg** (maximum Units per muscle)	Number of Injection Sites
Mandatory Ankle Muscles Gastrocnemius medial head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Gastrocnemius lateral head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Soleus	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Tibialis Posterior	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2

* did not exceed a total dose of 150 Units
** did not exceed a total dose of 300 Units

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

Statistically significant differences between BOTOX and placebo were demonstrated for the MAS and CGI for the 8 Units/kg dose only (see Table 47).

Table 47: Co-Primary Efficacy Endpoints Results in Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population)

	BOTOX 4 Units/kg (N = 125)	BOTOX 8 Units/kg (N=127)	Placebo (N=129)
Mean Change from Baseline in Plantar Flexors on the modified Ashworth Scale			
Week 4 and 6 Average	-1.01**	-1.06*	-0.80
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.49	1.65*	1.36

* Significantly different from placebo ($p<0.05$)
** Nominal p value <0.05

Compared to placebo, improvements in mean change from baseline for the MAS, and mean CGI score for lower limb spasticity were observed at timepoints up to Week 12 for BOTOX-treated patients (see Figure 17 and Figure 18).

Figure 17: Modified Ashworth Scale Ankle Score for Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) – Mean Change from Baseline by Visit

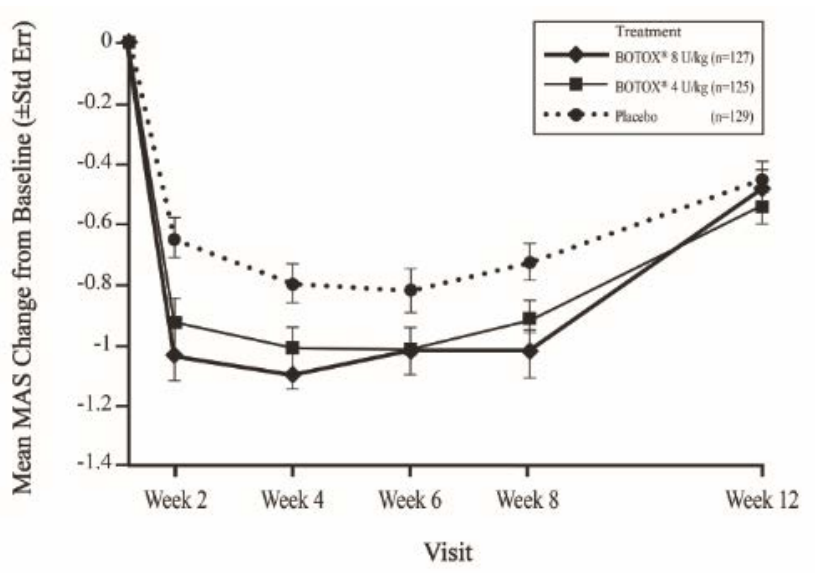
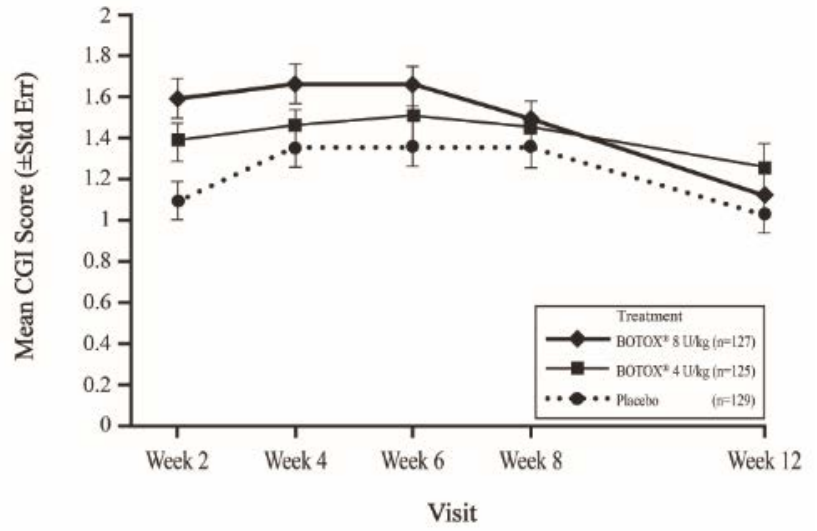


Figure 18: Clinical Global Impression of Overall Change for Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) – Mean Scores by Visit



14.7 Cervical Dystonia

A randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received BOTOX in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of BOTOX. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the

patients' status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 48.

Table 48: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

	Placebo (N=82)	BOTOX (N=88)	95% CI on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[a,b]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.
[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 49. The total dose and muscles selected were tailored to meet individual patient needs.

Table 49: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

Muscle	Number of Patients Treated in this Muscle (N=88)	Mean % Dose per Muscle	Mid-Range of % Dose per Muscle*
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

* The mid-range of dose is calculated as the 25th to 75th percentiles.

There were several randomized studies conducted prior to the double-blind, placebo-controlled study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of BOTOX.

14.8 Primary Axillary Hyperhidrosis

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who

scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities". A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group ($p<0.001$), but was not significantly different between the two BOTOX doses (see Table 50).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in BOTOX treated patients with either dose was 201 days. Among those who received a second BOTOX injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of BOTOX (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BOTOX group and 36% (28/78) in the placebo group, $p<0.001$. The difference in percentage of responders between BOTOX and placebo was 55% (95% CI=43.3, 65.9).

Table 50: Study 1 - Study Outcomes

Treatment Response	BOTOX 50 Units (N=104)	BOTOX 75 Units (N=110)	Placebo (N=108)	BOTOX 50-placebo (95% CI)	BOTOX 75-placebo (95% CI)
HDSS Score change ≥2 (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

14.9 Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of BOTOX at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

14.10 Strabismus
Six hundred seventy-seven patients with strabismus treated with one or more injections of BOTOX were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried powder supplied in a single-dose vial in the following sizes:
50 Units NDC 0023-3920-50
100 Units NDC 0023-1145-01
200 Units NDC 0023-3921-02

The top and bottom flaps of the BOTOX cartons have a tamper-evident seal that contains a translucent silver Allergan logo and the BOTOX vial labels have a holographic film that contains the name “Allergan” within rainbow colored horizontal lines (rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source to see the hologram). (Note: the holographic film on the label is absent in the date/lot area.) Each BOTOX vial label and carton also contains the U.S. License number: 1145 *[see Dosage and Administration (2.1)]*.

Do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time if the labeling is not described as above.

16.2 Storage and Handling
Unopened vials of BOTOX should be stored in a refrigerator between 2° to 8°C (36º to 46ºF) for up to 36 months. Do not use after the expiration date on the vial. Reconstituted BOTOX may be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caretaker to read the FDA-approved patient labeling (Medication Guide).

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms
Advise patients or their caretaker(s) to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens *[see Boxed Warning and Warnings and Precautions (5.1, 5.6)]*.

Ability to Operate Machinery or Vehicles
Advise patients or their caretaker(s) that if loss of strength, muscle weakness, blurred vision, dizziness, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Voiding Symptoms after Bladder Injections
After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan, Inc.
U.S. License Number 1145

Distributed by: Allergan USA, Inc.
Madison, NJ 07940

MEDICATION GUIDE
BOTOX®
BOTOX® Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for injection, for intramuscular, intradetrusor, or intradermal use

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening, including:

- **Problems breathing or swallowing**
- **Spread of toxin effects**

These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

- **Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.
  - People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
  - Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
  - loss of strength and muscle weakness all over the body
  - double vision, blurred vision and drooping eyelids
  - hoarseness or change or loss of voice (dysphonia)
  - trouble saying words clearly (dysarthria)
  - loss of bladder control
  - trouble breathing
  - trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines, crow's feet lines, and/or forehead lines.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat overactive bladder due to a neurologic disease in children 5 years of age and older when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in people 2 years of age and older with spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years of age and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine for adults that is injected into muscles and used for a short period of time (temporary) to improve the look of:

- moderate to severe frown lines between the eyebrows (glabellar lines)
- moderate to severe crow's feet lines
- moderate to severe forehead lines

You may receive treatment for frown lines, crow's feet lines, and forehead lines at the same time.

It is not known whether **BOTOX** is safe and effective in people younger than:

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm
- 2 years of age for treatment of spasticity

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe and effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe and effective for severe sweating anywhere other than your armpits.

It is not known if **BOTOX Cosmetic** is safe and effective for use more than 1 time every 3 months.

Who should not receive BOTOX or BOTOX Cosmetic?

Do not receive **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a complete list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as Myobloc®, Dysport®, or Xeomin®.
- have a skin infection at the planned injection site.
- are being treated for urinary incontinence and have a urinary tract infection (UTI).
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing).

What should I tell my doctor before receiving BOTOX or BOTOX Cosmetic?

Tell your doctor about all your medical conditions, including if you:

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- have allergies to any botulinum toxin product.
- had any side effect from any botulinum toxin product in the past.

- have or have had a breathing problem, such as asthma or emphysema.
- have or have had swallowing problems.
- have or have had bleeding problems.
- have plans to have surgery.
- had surgery on your face.
- have weakness of your forehead muscles, such as trouble raising your eyebrows.
- have drooping eyelids.
- have any other change in the way your face normally looks.
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence.
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months.
- have received injections of botulinum toxin, such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection.
- take muscle relaxants.
- take an allergy or cold medicine.
- take a sleep medicine.
- take anti-platelets (aspirin-like products) or anti-coagulants (blood thinners).

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How will I receive BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

What should I avoid while receiving BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic**. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth.
- discomfort or pain at the injection site.
- tiredness.
- headache.

- neck pain.
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- drooping eyebrows.
- urinary tract infection in both children and adults being treated for urinary incontinence.
- painful urination in adults being treated for urinary incontinence.
- bacteria in the urine of children being treated for urinary incontinence.
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.
- upper respiratory tract infection.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BOTOX and BOTOX Cosmetic:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for health professionals.

What are the ingredients in BOTOX and BOTOX Cosmetic?

Active ingredient: onabotulinumtoxinA

Inactive ingredients: human albumin and sodium chloride

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc.
U.S. License Number 1145
Distr buted by: Allergan USA, Inc. Madison, NJ 07940

Allergan

v5.0MG1145

This Medication Guide has been approved by the U.S. Food and Drug Administration. **Revised: 2/2021**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103000Orig1s5320

CROSS DISCIPLINE TEAM LEADER REVIEW

Summary Review

Date	July 26, 2021
From	Laura Jawidzik, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 103000 S-5320
Applicant	Allergan
Date of Submission	September 28, 2020
PDUFA Goal Date	July 28, 2020
Proprietary Name	Botox
Established or Proper Name	Onabotulinumtoxin A
Dosage Form(s)	Intramuscular injection
Applicant Proposed Indication(s)/Population(s)	N/A
Applicant Proposed Dosing Regimen(s)	Every 3 months
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	N/A
Recommended Dosing Regimen(s) (if applicable)	Additional dosing regimen that includes the brachialis, brachioradialis, pronator teres, pronator quadratus, flexor pollicis brevis, opponens pollicis, interossei, and lumbricals

1. Background

BOTOX is FDA-approved for the treatment of upper limb spasticity in adults and pediatric patients aged 2 years and older. Allergan submitted a supplemental biologics license application (sBLA) for Botox to support the dosing guidance for additional upper limb muscles within already approved muscle groups for the treatment of adult upper limb spasticity. The applicant has proposed the following muscles along with dosing guidance for inclusion into the already approved product labeling: brachialis, brachioradialis, pronator teres, pronator quadratus, flexor pollicis brevis, opponens pollicis, interossei, and lumbricals.

The Division had a pre-sBLA meeting with the applicant in June 2020. At that time, the Division agreed to review two double-blind, placebo-controlled trials in order to support the inclusion of dosing information for additional elbow flexors (brachialis, brachioradialis, pronator teres). The efficacy of BOTOX for additional hand and wrist muscles (e.g., opponens pollicis, flexor pollicis brevis, lumbricals/interossei muscles, pronator quadratus) was not studied in dedicated efficacy trials. The Division agreed to review data on the pharmacodynamic effect of injecting these muscles with BOTOX, in order to potentially describe dosing for these muscles in labeling.

2. Product Quality

N/A

3. Nonclinical Pharmacology/Toxicology

N/A

4. Clinical Pharmacology

N/A

5. Clinical Microbiology

N/A

6. Clinical/Statistical- Efficacy

Dr. Susanne Goldstein was the clinical reviewer for this application. Dr. Xiangmin Zhang was the biometrics reviewer, and Dr. Kun Jin was the biometrics team leader.

The following studies were reviewed to support the inclusion of the additional elbow flexor muscles (brachialis, brachioradialis, and pronator teres). These studies were reviewed by clinical reviewer Dr. Susanne Goldstein, and statistician Dr. Xiangmin Zhang.

Study	Design	Duration	Treatment Arms (No. of patients)	Population
GSK-207660	Randomized, double-blind, placebo-controlled with open-label extension	One double-blind treatment, with 12-week follow-up, followed by 3 open-label treatments	PBO+ BOTOX 240 U (63) BOTOX 400 U (61)	Stroke patients with upper extremity spasticity
191622-127	Randomized, double-blind, placebo-controlled	One double-blind treatment with 12-week follow-up	PBO (18) BOTOX 300 U (18) BOTOX 500 U (17)	Stroke patients with upper extremity spasticity

The data from the following study was reviewed for descriptive purposes only in order to support the dosing for inclusion of additional hand and wrist muscles (pronator quadratus, flexor pollicis brevis, opponens pollicis, lumbricals, and interossei). These data were reviewed by Dr. Susanne Goldstein.

Study	Design	Duration	Treatment Arms (No. of patients)	Population
191622-057	Randomized, double-blind, placebo-controlled safety study	Two treatment cycles	PBO BOTOX 240 U or 360 U	Stroke patients with respiratory compromise

A. Study GSK-207660

Study GSK-207660 was a multicenter, double-blind, randomized comparative study of BOTOX 240 U vs BOTOX 400 U in patients with post-stroke upper limb spasticity. Patients received a single treatment with BOTOX either 240 U or 400 U in the double-blind period and then continued into the open-label portion of the study where they received three additional treatments with 400 U. In the double-blind period, patients in the 240 U arm were given placebo in the elbow flexors (Table 1) and patients in the 400 U arm were given 160 U in the elbow flexors in order to assess efficacy of BOTOX in those muscles.

Table 1 Study GSK-207660: Muscles and Doses to be Injection in the Blinded Period

Joint	Muscle	BOTOX 400 U	BOTOX 240 U/PBO
Elbow	Biceps brachii	70	PBO
	Brachialis	45	PBO
	Brachioradialis	45	PBO
Wrist	Flexor carpi radialis	50	50
	Flexor carpi ulnaris	50	50
Finger	Flexor digitorum profundus	50	50
	Flexor digitorum superficialis	50	50
Thumb	Flexor pollicis longus	20	20
	Adductor pollicis	20	20
Total		400	240

Source: Adapted from CSR from Study GSK-207660

Demographic characteristics of randomized patients were similar across the two treatment groups. More males (80%) than females (20%) were randomized into the study.

The primary endpoint of the study was the proportion of patients whose Modified Ashworth Scale (MAS) score for the elbow muscles was decreased by at least 1 level from baseline at week 6. The MAS scores of 0, 1, 1+, 2, 3, or 4 were coded as 0, 1, 2, 3, 4, or 5, respectively.

The results of the primary endpoint are presented in Table 2. The responder rate on the MAS score reduction in the elbow flexors at week 6 was higher in the BOTOX 400 U group than in the BOTOX 240 U group. Patients missing the week 6 assessment were considered non-responders.

Table 2 Study GSK-207660: Analysis of MAS Responder Rate

Treatment	N	Responder/n (%)	Difference from 240 U (%)	95% CI (%)
GSK1358820 240 U	63	32/63 (50.8%)	18.1	(1.1, 35.0)
GSK1358820 400 U	61	42/61 (68.9%)		

Source: statistical review

The applicant also presented the change from baseline in MAS score for the elbow flexors (Table 3). This table displays the estimated differences between the BOTOX 400 U group and the BOTOX 240 U group at Weeks 2, 4, 6, and 12. The nominal p-values for testing these treatment differences were 0.0005, 0.0048, 0.027, and 0.0329, respectively.

Table 3 Study GSK-207660: Analysis of Change from Baseline in MAS Score

Joint Visit	GSK1358820 240 U			GSK1358820 400 U			Difference from 240 U[1]	95% CI for Treatment Difference
	N (n)	Adjusted Mean	S.E. of Adjusted Mean	N (n)	Adjusted Mean	S.E. of Adjusted Mean		
Spasticity Gr-Elbow Flexion								
PERIOD 1 - V2 (Week 2)	63 (63)	-0.59	0.089	61 (60)	-1.07	0.102	-0.48	(-0.75, -0.22)
PERIOD 1 - V3 (Week 4)	63 (63)	-0.7	0.097	61 (59)	-1.12	0.110	-0.42	(-0.71, -0.13)
PERIOD 1 - V4 (Week 6)	63 (63)	-0.71	0.107	61 (59)	-1.09	0.128	-0.37	(-0.71, -0.04)
PERIOD 1 - V5 (Week 12)	63 (60)	-0.35	0.072	61 (57)	-0.61	0.101	-0.27	(-0.51, -0.02)

Source: statistical review

B. Study 191622-127

Study 191622-127 was a multicenter, randomized, double-blind, 3-arm, parallel group study of BOTOX 300 U and BOTOX 500 U compared to placebo. Patients received a single treatment cycle of either BOTOX 300 U, BOTOX 500 U, or placebo. Patients receiving 300 U received 150 U in the elbow muscles and 150 U in the shoulder muscles. Patients randomized to 500 U received 250 U in the elbow muscles and 250 U in the shoulder muscles. Patients were randomized 1:1:1 and stratified by baseline spasticity.

Table 4 Study 191622-127: Muscles and Doses to be Injected in the Blinded Period

Joint	Muscle	BOTOX 300 U	BOTOX 500 U
Elbow	Biceps brachii	60	100
	Brachialis	30	50
	Brachioradialis	45	75
	Pronator teres	15	25
Total Elbow		150	250
Shoulder	Pectoralis major	75	125
	Teres major	30	50
	Latissimus dorsi	45	75
Total		150	250

Source: clinical review

The study was terminated early by the applicant for administrative reasons. This led to a markedly reduced sample size. A total of 53 patients completed the study, out of a planned 453 patients.

The efficacy analysis population was the intention-to-treat (ITT) population consisting of all randomized patients. The primary efficacy analysis was the change from baseline in the modified Ashworth Scale-Bohannon (MAS-B) at week 6 (Table 5). The least squares mean difference between BOTOX 500 U and placebo was -0.88, with a nominal p-value of 0.048, and the difference between BOTOX 300 U and placebo was -0.73, with a nominal p-value of 0.094.

Table 5 Study 191622-127: Primary Endpoint Change from Baseline in MAS-B

Visit	Statistics	BOTOX 500 U (N=17)	BOTOX 300 U (N=18)	Placebo (N=18)	BOTOX 500 U vs. Placebo P-value Difference 95% CI[a]	BOTOX 300 U vs. Placebo P-value Difference 95% CI[a]
Baseline	N	17	18	18		
	Mean	4.12	4.06	4.17		
	SD	0.332	0.236	0.383		
	Median	4.00	4.00	4.00		
	Min, Max	4.0, 5.0	4.0, 5.0	4.0, 5.0		
Week 6	N	16	18	17	0.048	0.094
	LS Mean[a]	-1.62	-1.47	-0.74	-0.88	-0.73
	Mean	-1.63	-1.44	-0.76	(-1.75, -0.01)	(-1.58, 0.13)
	SD	1.455	1.247	0.970		
	Median	-1.00	-1.00	0.00		
	Min, Max	-4.0, 0	-3.0, 0	-3.0, 0		

Source: statistical review

Dr. Goldstein and Dr. Zhang have concluded that studies GSK-207660 and 191622-127 support the addition of dosing information for brachialis, brachioradialis, and pronator teres to the product labeling. (b) (4)

C. Support for Additional Hand and Wrist Muscles

Study 191622-057:

This was a phase 2, multicenter, double-blind, randomized, placebo-controlled safety study to evaluate the pulmonary function of patients with compromised baseline respiratory status. Patients were randomized to either placebo, BOTOX 240 U, or 360 U. Muscle tone of the affected flexor muscles was measured as a secondary endpoint, using the Ashworth scale.

Dr. Goldstein described the responder rates on the Ashworth for the subsets of patients who were injected into a given muscle (Table 6). These are post hoc analyses from Study 191622-057. A responder definition of a 1-point or more change from baseline on the Ashworth is considered clinically meaningful.

Table 6 Study 191622-057: Change in Ashworth Score (Responder Analysis)-Baseline to Week 6

		<1	≥1 to ≤ 2	≥2	Total Responders	Dose range for responders
Pronator Quadratus	360 U (N=10)	2 (20%)	5 (50%)	0	**7 (70%)**	10-40 U
	240 U (N=14)	5 (36%)	7 (50 %)	2 (14%)	**9 (64%)**	10-20 U
	Placebo (N=14)	9 (64 %)	5 (36 %)	0	**5 (36%)**	
FPB/OP	360 U (N=15)	7 (47%)	7 (46%)	1 (7%)	**8 (53%)**	10-25 U
	240 U (N=13)	4 (31%)	8 (61%)	1 (8%)	**9 (69%)**	7-27 U
	Placebo (N=15)	10 (67%)	5 (33%)	0	**5 (33%)**	
Lumbricals/IO	360 U (N=4)	3 (75%)	1 (25 %)	0	**1 (25%)**	10 U
	240 U (N=4)	2 (50 %)	2 (50%)	0	**2 (50%)**	7-33 U
	Placebo (N=6)	4 (67 %)	2 (33 %)	0	**2 (33%)**	

Source: clinical review

Data from Study 191622-057 supported the inclusion of the pronator quadratus, flexor pollicis brevis, and opponens pollicis in the product labeling. There was no clear dose response to support the inclusion of the interossei and lumbricals into the label using the responder analysis from this study.

During labeling negotiations, the applicant provided additional information to support the inclusion of the lumbricals and interossei into the product labeling. The applicant combined the two dosing groups for the lumbricals/interossei from Study 191622-057 and analyzed the change from baseline to week 6 on the Ashworth for the combined group, as compared to placebo. There was a slight trend towards improvement in mean change from baseline at week 6 on the Ashworth in the combined BOTOX group as compared to placebo (-0.38 vs -0.33). Additionally, when combining the dosing groups, the responder analysis shown in Table 6 becomes 3/8 (37.5%) vs 2/6 (33%) in favor of BOTOX. Although the numerical treatment effect is modest, the strong prior of the efficacy of BOTOX for the treatment of spasticity across multiple muscle groups support a description of doses to be used for injection of the interossei and lumbricals in labeling.

Summary of Additional Muscles and Study Source for Dosing Recommendations

Muscle	Recommended Dose Total Dosage (Number of Sites)	Study
Biceps Brachii	60 Units to 200 Units divided in 2-4 sites	Already in label
Brachioradialis	45 Units to 75 Units divided in 1-2 sites	GSK-207660; 191622-127
Brachialis	30 Units to 50 Units divided in 1-2 sites	GSK-207660; 191622-127
Pronator Teres	15 Units to 25 Units in 1 site	191622-127
Pronator Quadratus	10 Units to 50 Units in 1 site	191622-057
Flexor Carpi Radialis	12.5 Units to 50 Units in 1 site	Already in label
Flexor Carpi Ulnaris	12.5 Units to 50 Units in 1 site	Already in label
Flexor Digitorum Profundus	30 Units to 50 Units in 1 site	Already in label
Flexor Digitorum Sublimis	30 Units to 50 Units in 1 site	Already in label
Lumbricals/Interossei	5 Units to 10 Units in 1 site	191622-057
Adductor Pollicis	20 Units in 1 site	Already in label
Flexor Pollicis Longus	20 Units in 1 site	Already in label
Flexor pollicis brevis/ Opponens pollicis	5 Units to 25 Units in 1 site	191622-057

7. Safety

The current FDA-approved label for BOTOX indicates that the total dose of BOTOX in a 3-month interval should not exceed 400 U. At the pre-BLA meeting for this supplement, the Division agreed that no additional safety information for 400 U of BOTOX was needed for the treatment of spasticity in adults. Dr. Goldstein reviewed the safety analyses presented in the clinical study reports for studies GSK-207660 and 191622-127. No new safety issues were identified during the review of this supplement.

8. Pediatrics

N/A

9. Other Relevant Regulatory Issues

N/A

10. Labeling

- DOSAGE AND ADMINISTRATION:

  - Table 4 in Section 2 and the corresponding Figure 2 in Section 2 for adult upper limb spasticity have been updated to include the following muscles with their corresponding dose range: brachioradialis, brachialis, pronator teres, pronator quadratus, lumbricals/interossei, flexor pollicis brevis, and opponens pollicis.

- CLINICAL STUDIES section:
  - Section 14 has been updated to include a description of the results of study GSK-207660. The p-value for the mean change analysis is nominal only, and this will be noted in the label.

11. Postmarketing Recommendations

N/A

12. Recommendations

The efficacy of BOTOX for the treatment of adult upper limb spasticity was previously demonstrated in no fewer than 5 clinical trials. This supplement proposes the addition of 8 muscles within the already approved muscle groups for the treatment of upper limb spasticity. These muscles and their dosing range should be added to Section 2. The current FDA-approved label for BOTOX indicates that the total dose of BOTOX in a 3-month interval should not exceed 400 U. No changes to the total maximum recommended dose will be made based on the studies included in this supplement, and no new safety information will be added to the label.

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LAURA A JAWIDZIK
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103000Orig1s5320

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	103000 5320
Priority or Standard	Standard
Submit Date(s)	September 28, 2020
Received Date(s)	September 28, 2020
PDUFA Goal Date	July 28, 2020
Division/Office	OND/DN1
Reviewer Name(s)	Susanne R. Goldstein M.D.
Review Completion Date	July 20, 2021
Established/Proper Name	Onabotulinumtoxin A
(Proposed) Trade Name	BOTOX
Applicant	Allergan
Dosage Form(s)	Intramuscular injection
Applicant Proposed Dosing Regimen(s)	Every 3 months
Applicant Proposed Indication(s)/Population(s)	Adult upper limb spasticity
Recommendation on Regulatory Action	Approval: Addition of brachialis, brachioradialis, pronator teres, pronator quadratus, flexor pollicis brevis/opponens to the label
Recommended Indication(s)/Population(s) (if applicable)	Adult upper limb spasticity

Table of Contents

Table of Tables

No table of figures entries found.

Table of Figures

No table of figures entries found.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

BOTOX (Onabotulinumtoxin) is a sterile, vacuum dried, purified, botulinum toxin type A produced from fermentation of Hall strain Clostridium botulinum toxin type A and purified to a complex of the neurotoxin and several accessory proteins.

BOTOX blocks the neuromuscular transmission by binding to acceptor sites on the motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. BOTOX is approved for the treatment of Strabismus, Blepharospasm, Cervical Dystonia, Overactive Bladder, Chronic Migraine, Upper Limb Spasticity, Lower Limb Spasticity, Primary Axillary Hyperhidrosis, and Glabellar Frown Lines.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted two new double-blind, placebo-controlled trials, GSK 207660 and 191622-127, examining the efficacy of injecting brachialis, brachioradialis and pronator teres for the treatment of upper limb spasticity in adults. Study GSK207660 demonstrated clinically meaningful treatment effect on upper limb spasticity for brachioradialis and brachialis muscles. Study 191622-127, which was terminated early for administrative reasons, demonstrated a clinically meaningful effect, although nominally significant, on upper limb spasticity for brachioradialis, brachialis and pronator teres.

In addition, the Applicant submitted double-blind and open-label summary data from 4 legacy studies in support of adding distal upper extremity muscle dosing information to the label. The summary data from double-blind placebo-controlled trials (exposure, dosing recommendations) is considered adequate for the addition of pronator quadratus, flexor pollicis brevis/opponens and lumbricals/interossei to include in labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Spasticity is a chronic condition common to many neurological disorders (stroke, multiple sclerosis, cerebral palsy, traumatic brain injury, spinal cord injury and neurodegenerative diseases) and often leads to discomfort/pain and interferes with activities of daily living. Treatment of upper limb spasticity with neurotoxins, specifically botulinum toxins, has been shown to be effective and has been approved for three of the marketed toxins. The presentation (pattern) of upper limb spasticity is variable between patients, requiring flexibility in muscles to be injected. The inclusion of additional upper limb muscles is supported by the treatment effect demonstrated in the double-blind studies. No new safety signals have been identified.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Spasticity is a chronic condition that has been defined as a "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting an intermittent or sustained involuntary activation of muscles." (Burridge 2005). • It is common in many neurological disorders including stroke, multiple sclerosis, cerebral palsy, spinal cord injuries, traumatic brain damage, and other neurodegenerative diseases (Roze 2012; Pandey 2019). • In adults, stroke is the most common cause of spasticity (Sheean 2006). • It has been estimated in 2 unique studies that approximately 40% of poststroke patients eventually develop some degree of spasticity (Urban 2010; Watkins 2002), which translates into approximately	Characteristics of spasticity include muscle stiffness, paresis, muscle spasms, muscle fatigue, and change in limb posture. Abnormal posture of the arm, wrist, and hand due to the intermittent or sustained involuntary contraction of muscles in the arm, as well as dysfunction of the shoulder and elbow muscles, are features of upper limb spasticity. This muscle activity is not only a discomfort to the patient but interferes with activities of daily living (e.g., dressing, bathing, feeding, grooming), personal hygiene and often contributes to the need for full time care as the patient's ability to carry out simple tasks is greatly reduced. Furthermore, those with spasticity are at increased risk of secondary

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2.3 million adults in the US.	limb deformities that further increase disability (e.g., reduced mobility, difficulty with self-care, and hygiene), and complications (e.g., infection, malodor).
Current Treatment Options	• Insert text as bullets (recommended) There are three neurotoxins approved for the treatment of upper limb spasticity: Onabotulinumtoxin A abobotulinumtoxin A incobotulinumtoxinA	Presentation of upper limb spasticity is variable across patients. Including additional muscles with dosing recommendations could further improve the treatment effect of onabotulinumtoxin A in patients with upper limb spasticity.
Benefit	• In Study GSK207660, the responder rate on the MAS score reduction in the elbow flexors at Week 6 after the first treatment was higher in the BOTOX 400 units group (68.9%, 42/61 subjects) than in the BOTOX 240 units group (50.8%, 32/63 subjects). The difference between the treatment groups was 18.1% (95% CI, 1.1 to 35.0) • In Study 191622-127, both Botox groups had higher responder rates than the placebo group. Nominal p-values for the Botox-placebo comparisons using the chi-square test were 0.101 and 0.129 for the Botox 500 U group and Botox 300 U group, respectively.	Clinically meaningful treatment effect was demonstrated in the double-blind placebo-controlled studies presented in the submission.
Risk and Risk Management	The most common treatment emergent adverse events were upper respiratory (nasopharyngitis, bronchitis, pneumonia.)	The safety of the 400 U maximum dose was previously established for adult upper limb spasticity (BLA 103000/5282, approved April 17, 2015). In comparison, the GSK 207660 and 191622-127 studies do not provide any new safety signals, and the overall safety profile is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		consistent with that of the demonstrated safety of 400 U BOTOX.

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2. Therapeutic Context

2.1. Analysis of Condition

Spasticity is a chronic condition that has been defined as a "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting an intermittent or sustained involuntary activation of muscles." It is common in many neurological disorders including stroke, multiple sclerosis, cerebral palsy, spinal cord injuries, traumatic brain damage, and other neurodegenerative diseases. In adults, stroke is the most common cause of spasticity. It has been estimated in 2 unique studies that approximately 40% of poststroke patients eventually develop some degree of spasticity), which translates into approximately 2.3 million adults in the US.

In the upper extremity, common patterns of spasticity include clenched fist, thumb-in-palm, flexed wrist/pronated forearm, flexed elbow, and adducted/internally rotated shoulder. These deformities/abnormal postures are caused by marked muscle overactivity of the flexor muscles, leading to significant disability and disease burden. Other patterns may manifest, and most cases do not present as a single entity but in combination.

2.2. Analysis of Current Treatment Options

In the US, four injectable botulinum neurotoxin (BoNT) products are available. Three of the neurotoxins are approved for the treatment of Upper Limb Spasticity (BOTOX, Dysport, Xeomin.)

Table 1 FDA approved botulinum toxins

Botulinum Neurotoxin	Trade Name	Indication
Onabotulinumtoxin A	BOTOX® (also Botox Cosmetic®)	Cervical Dystonia, Blepharospasm, Strabismus, Glabellar frown lines, Primary Axillary hyperhidrosis, Upper limb spasticity, Lower limb spasticity, Chronic migraine,

		Overactive Bladder
rimabotulinumtoxin B	Myobloc®	Cervical Dystonia Sialorrhea
abobotulinumtoxin A	Dysport®	Cervical Dystonia, Glabellar frown lines, Upper limb spasticity, Lower limb spasticity
incobotulinumtoxinA	Xeomin®	Cervical Dystonia, Blepharospasm, Glabellar frown lines, Upper limb spasticity, Sialorrhea

Source: Clinical Reviewer

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Botox was first approved on December 29, 1989, in the US for treatment of strabismus. Since the initial approval, additional indications have been approved including the treatment of: blepharospasm, seventh cranial nerve disorders, cervical dystonia, upper and lower limb spasticity in adults and pediatric patients, primary focal axillary hyperhidrosis, urinary incontinence due to neurogenic detrusor overactivity, overactive bladder, and prophylaxis of chronic migraine.

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-sBLA meeting was held with the Applicant, on June 4, 2020, to discuss:

1. Additional elbow flexors (brachialis, brachioradialis, and pronator teres), based on currently available controlled clinical study data (studies GSK207660 and 191622-127), and

2. Additional muscles, many of which have complementary and/or synergistic motions with approved muscle groups of the upper limb, based on double-blind, placebo-controlled and open-label clinical studies that included BOTOX treatment of these muscles.

Key discussion points from the Meeting Minutes (June 30, 2020) are summarized below:

- On face, studies GSK 207660 and 191622-127 may support review of a supplement to add dosing information for additional elbow flexors.

- The sBLA should include evidence to support that the treatment effect (assessed by the change in Ashworth Scale scores) on the additional elbow flexor muscles is, at a minimum, as high as the effect reported in the other upper extremity muscles currently described in section 14 of the Botox labeling.

- The Division agreed that the change in Ashworth Scale score and the responder rate would support review of the Sponsor's sBLA to add dosing information to additional
- elbow flexor muscles.

- Additional safety information is not needed for the treatment of spasticity in adults (excluding the shoulder muscles) with a maximum dose of 400 U.

- Analyses of efficacy should be presented as the change from baseline in the MAS score to the primary endpoint visit and the clinician global assessment, for patients treated in the additional elbow flexors. In addition, include an analysis of patients who had at least a one-point improvement on the MAS compared to baseline at the primary
- endpoint visit.

- In order to provide dosing guidance in the label for other upper limb, the Division would want to see data on the pharmacodynamic effect of injecting these muscles with Botox. The Sponsor has data on approximately 80 subjects treated with Botox in the hand muscles, although specific dosing would not be available, only a range of doses used. The Division recommended that the Sponsor include the data in the proposed sBLA along with proposed dosing, which will be reviewed by the Division.

4. Sources of Clinical Data and Review Strategy

4.1. **Table of Clinical Studies**

Studies supporting additional elbow flexor muscles (brachialis, brachioradialis, pronator teres)

Table 2 Design Features of Clinical Efficacy Studies Supporting Registration of Additional Elbow Flexors

Study Number	Study Design	Study Treatment	Number of Patients Entered/ Completed	Duration/ No. of Treatments	Endpoints
GSK 207660	Phase 3, multicenter, double-blind, randomized, parallel-group, placebo-controlled Followed by an OL phase	DBPC Phase: IM injections in fingers, thumb, wrist, and elbow muscles: • BOTOX 400 U (240 U fingers, thumb, wrist + 160 U elbow flexors) • BOTOX 240 U (fingers, thumb, wrist) + Placebo (160 U elbow flexors) OL Phase: BOTOX 400 U divided among affected upper limb muscles	DBPC: BOTOX 400 U: 63/63 BOTOX 240 U/ Placebo: 61/61 OL: BOTOX 400 U: 124/113	48 weeks: 1 DBPC treatment with 12 weeks follow-up, followed by up to 3 OL treatments at 12-week retreatment intervals	• The proportion of the patients in whom MAS-B score was reduced at least 1 from baseline in the elbow flexors (the responder rate). • The responder rate of MAS-B score reduction in finger, thumb and wrist flexors • Changes in MAS-B score from baseline in finger, thumb, wrist and elbow flexors • Changes in DAS (principal therapeutic target) from baseline • Safety

191622-127	Phase 3, multicenter, double-blind, randomized, parallel-group, placebo-controlled	IM injections in elbow and shoulder muscles: • BOTOX 300 U (150 U elbow; 150 U shoulder) • BOTOX 500 U (250 U elbow; 250 U shoulder) • Placebo	BOTOX 500 U: 17/17 BOTOX 300 U: 18/18 Placebo: 18/18	1 treatment with 12 - 16 weeks follow-up	• Change from baseline in MAS-B for elbow flexors • Change from baseline in MAS-B of the shoulder adductors • Change from baseline in CGI by Physician • Change in DAS • Change in Pain scale (11-point numeric rating scale) • Safety

Source: Sponsor

Studies supporting additional wrist/forearm and thumb/finger muscles (pronator quadratus, flexor pollicis brevis/opponens, lumbricals/interossei)

Table 3 Design Features of Clinical Efficacy Studies Supporting Registration of Additional Upper Limb Muscles

Study Number	Study Design	Study Treatment	Number of Patients Entered/ Completed	Duration/ No. of Treatments	Endpoints

191622-057	Phase 2, multicenter, DBPC, parallel group	IM injections in the upper limb muscles: • BOTOX 240 U • BOTOX 360 U • Placebo	BOTOX 360 U: 55/51 BOTOX 240 U: 52/47 Placebo: 48/42	Up to 2 treatments 12 to 18 weeks apart	• Change from baseline and percent change from baseline in pulmonary function tests, FEV1, FVC, and the derived variable FEV1/FVC • Muscle tone of the affected flexor muscles of the designated upper limb (elbow, wrist, fingers, and thumb) on the AS
AGN/HO/SPA/001 - 191622 (BEST)	Phase 3b, multicenter, double-blind, randomized, placebo-controlled Followed by an OL phase	IM injections into upper and/or lower limb muscles. BOTOX dose per investigator's discretion Part 1 (DBPC): Patients randomized 1:1 to: • BOTOX plus SC • Placebo plus SC	DBPC: BOTOX: 139/131 Placebo: 135/122 OL: BOTOX/BOTOX: 113/112 Placebo/BOTOX: 112/106	DBPC: Up to 2 treatments with 22 to 34 weeks follow-up OL: Up to 4 treatments with 18 to 30 weeks follow up	• Attainment of the principal active functional goal as assessed by the physician, measured as a score of 0 to +2 on the GAS • Principal active functional goal attainment, as assessed by the physician and patient • The principal and secondary functional GAS scores as assessed by the physician and patient • The time to principal and secondary functional goal attainment • Safety
191622-056	Phase 2, multicenter, OL	IM injections in the elbow, forearm, wrist, fingers, thumb, and hand • BOTOX 200-400 U	BOTOX 200-400 U: 279/226	Up to 5 treatments over a 54-week period with ≥ 12 weeks between	• Flexor tone of the elbow, wrist, finger, and thumb flexors as measured by AS • Improvement in functional disability using DAS • Improvement in PGA • Safety

				treatments	
GMA-BTX-SP-12-001 (ASPIRE)	Phase 4, multicenter, OL, prospective, observational	As per usual practice	BOTOX: 731/467	Up to 8 treatments over 96 weeks with 12 weeks follow-up/treatment	• Determine the patterns of utilization of BOTOX as a treatment for spasticity in actual clinical practice • Quantify the effectiveness of BOTOX as measured by patient reported and physician reported treatment satisfaction for treatment of spasticity in actual clinical practice • Safety

Source: Sponsor

4.2. **Review Strategy**

The application presents efficacy and safety data supporting the use of BOTOX® to add dosing guidance for **8 additional upper limb muscles** within the already approved muscle groups of adult upper limb spasticity (sBLA 103000/ 5189 and 5252).

The additional **elbow flexors include brachialis, brachioradialis, and pronator teres**, evaluation of efficacy for elbow spasticity, is based on results of two new studies that were not previously submitted to this BLA:

- **Study GSK 207660**: A Phase 3, multicenter, double-blind, randomized, placebo-controlled study, with an OLextension, evaluating the efficacy and safety of BOTOX in patients with poststroke upper limb spasticity
- **Study 191622-127**: A Phase 3, multicenter, double-blind, randomized, placebo-controlled, parallel-group single treatment cycle study of the safety and efficacy of BOTOX for the treatment of spasticity involving the muscles of the elbow and shoulder in adult poststroke patients

The evaluation of efficacy for additional upper limb muscles, contributing to the spasticity of the **wrist/forearm, fingers, and thumb** is based on two legacy DBPC Allergan studies, with support from an OL study, which have been previously submitted to the Agency as noted below:

- **Study 191622-057:** A Phase 2, multicenter, double-blind, randomized, placebo-controlled study with up to 2 treatment cycles of placebo or BOTOX (BLA 103000/eCTD SN0023, submitted 20 August 2008). Study 191622-057 was previously reviewed by Dr. Ramesh Raman (sBLA 103000/5189, May 2009).

- **Study AGN/HO/SPA/001-191622 (BOTOX Economic Spasticity Trial [BEST]):** A Phase 3b, multicenter, randomized, placebo-controlled study of placebo or BOTOX combined with standard of care, followed by an OL extension (BLA 103000/eCTD SN0157 submitted 30 March 2012). Study AGN/HO/SPA/001-191622 was previously reviewed by Dr. Gerald D. Podskalny for lower limb spasticity (sBLA 103000/5252, January 28, 2013.)

- **Study 191622-056:** A Phase 2, multicenter, OL study of the safety of repeated treatments of BOTOX for the treatment of focal upper limb poststroke spasticity (BLA 103000/eCTD SN0023). Study 191622-056 was previously reviewed by Dr. Ramesh Raman (sBLA 103000/5189, May 2009).

A Phase 4 study, **GMA-BTX-SP-12-001 (ASPIRE)**, which describes "real-world" BOTOX injections of these muscles, is included in the application. Due to the uncontrolled nature of the study, it is not considered to be supportive of efficacy or safety.

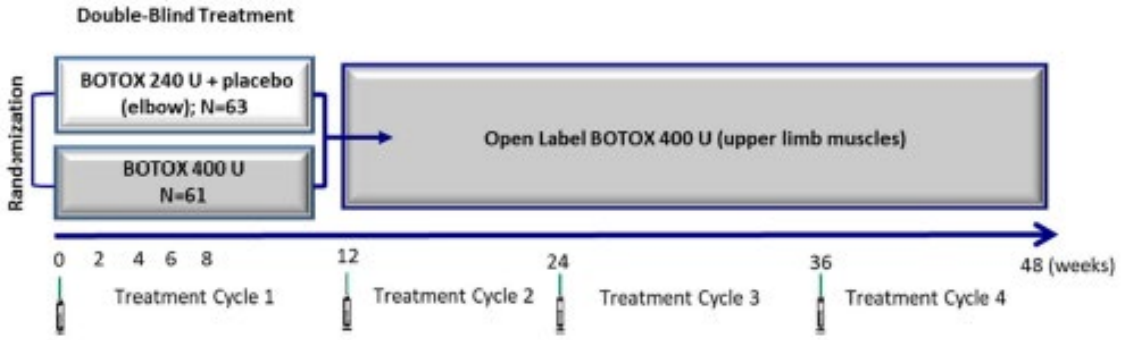
5. Review of Relevant Individual Trials Used to Support Efficacy

5.1. GSK 207660 Phase 3 multicenter, double-blind, randomized comparative study and open-label, uncontrolled study to evaluate the efficacy and safety of GSK1358820 in patients with post-stroke upper limb spasticity

5.1.1. Study Design

The trial design is outlined in the figure below.

Figure 1 Study Design of GSK 207660



Source: Sponsor

Overview and Objective

To evaluate the efficacy of the injections of 400 units of the product at Week 6 (finger/ wrist flexors: 240 units, elbow flexors: 160 units), comparing to that of 240 units (finger/ wrist flexors: 240 units, elbow flexors: placebo).

Dosing

Dosing for each muscle during the double-blind phase of the study is outlined in the table below.

Table 4 Study GSK 207660: Muscles and Doses to be Injected in the Blind Phase

Joint	Muscles	BOTOX 400 U Dose (units)	BOTOX 240 U / Placebo Dose (units)	Number of injection sites (sites/muscle)[c]
Elbow	Biceps brachii	70[a]	Placebo	2
	Brachialis	45[a]		1
	Brachioradialis	45[a]		1
Wrist	Flexor carpi radialis	50[b]	50[b]	1
	Flexor carpi ulnaris	50[b]	50[b]	1
Finger	Flexor digitorum profundus	50[b]	50[b]	1
	Flexor digitorum superficialis	50[b]	50[b]	1
Thumb	Flexor pollicis longus	20[b]	20[b]	1
	Adductor pollicis	20[b]	20[b]	1
Total		400	240	-

[a] Within the limits of the total of 160 U (the elbow flexors), the dose could be adjusted by the investigator
[b] Within the limits of the total of 240 U (the finger, thumb and wrist flexors), the dose could be adjusted by the investigator
[c] When the dose would exceed 50 U per muscle, the investigator was to consider the divided injections. Source: Module 5.3.5.1, CSR GSK 207660, Table 3

Source: Sponsor

Study Endpoints

Primary endpoint:

- The rate of the subjects that that Modified Ashworth Scale (MAS) score was reduced at least 1 from the baseline in the elbow flexors (responder rate)

Secondary endpoints:

- The responder rate of MAS score from baseline in finger, thumb and wrist flexors
- Changes in MAS score from baseline in finger, thumb, wrist, elbow, pronation of forearms and shoulder flexors, 400 U BOTOX versus 240 U BOTOX
- Changes in Disability Assessment Scale (DAS) from baseline

Exploratory endpoints:

- Change in MAS score from baseline in finger, thumb, wrist, elbow, pronation of forearm and shoulder muscles, BOTOX 400 U
- Changes in Numeric Rating Scale (BRS) for pain from baseline
- Changes in other items of DAS from baseline
- Clinical Global Impression of Change(CGI) of functional disability by an investigator
- CGI of functional disability by a patient
- Time to patient-reported onset of spasticity symptom relief
- Patient-reported benefit of injection
- Time to qualification for retreatment
- Testing for neutralizing antibody

Statistical Analysis Plan

The Primary efficacy analyses were performed based on ITT1 Population (all subjects who were randomized in the study and who had at least 1 post-baseline efficacy assessment), unless otherwise specified. The intergroup difference (400 units – 240 units) in the MAS responder rate of the elbow flexors at Week 6 and the associated 95% confidence interval (CI, Wald type) was calculated. The responder rate was defined as the proportion of subjects whose MAS score decreased by at least 1 level from the baseline in the ITT1 Population, that was if MAS score of a given subject was missing, then this subject was regarded as a non-responder.

The MAS scores for all the joints were calculated by counting the scores 0, 1, 1+, 2, 3 and 4 as 0, 1, 2, 3, 4 and 5, respectively, unless otherwise specified

Subgroup analyses were performed using Baseline MAS score in the elbow flexors (randomization stratum) and rehabilitation use. The difference in the responder rate and the associated 95% CI were calculated in the same manner as for the primary efficacy analyses.

The Secondary efficacy analyses were performed based on ITT1 Population, unless otherwise specified. The Secondary efficacy analyses were performed for only the double-blind phase. Unless otherwise specified, the data up to Week 12 from the first treatment was used for statistical analyses to avoid the potential selection bias caused by retreatment and dropout from double-blind phase.

MAS Scores in the Elbow, Finger, Thumb and Wrist Flexors

Values and changes from baseline were summarized using mean, standard deviation (SD), 95% CIs, median, minimum and maximum by visit, treatment group and joint.

A mixed model for repeated measures (MMRM) was fitted to changes from baseline. This model included treatment, visit and treatment-by-visit interaction as categorical fixed effect and baseline value and baseline-by-visit interaction as continuous fixed effect. An unstructured variance structure was used to model the within-subject errors. In addition, an empirical sandwich estimator was used to estimate the standard errors (SEs). Adjusted means and the corresponding SEs of adjusted means were presented. Moreover, estimated treatment differences and the corresponding 95% CI were presented.

Responder Rate of MAS in the Elbow, Finger, Thumb and Wrist Flexors

Responder rate was defined as the proportion of the subjects whose MAS score decreased by at least 1 level from baseline in ITT1 Population, except for the subject of which joint was not evaluable. The unevaluable joint for MAS score was the joint which was not administered. The intergroup difference (400 units – 240 units) in the responder rate and associated 95% CI were calculated in the same manner as for the primary efficacy analyses. In addition, Mantel-Haenszel method was conducted for these endpoints using Baseline MAS score in the elbow flexors, regardless of the corresponding MAS score in the other joints.

Protocol Amendments

MAY-24-2017 Amendment 01

- Add pulse oximeter oxygen saturation (SpO2) in Eligibility Criteria Requested by PMDA

OCT-06-2017 Amendment 02

- Delete laboratory data from the Eligibility Criteria for Retreatment in and after Treatment Cycle 2, and add eligibility criteria regarding the SpO2 GSK1358820 is unlikely to affect laboratory test data. Specify the acceptable range of SpO2 values.
- Add a description regarding the SpO2 Specify the acceptable range of SpO2 values to ensure the safety.
- Add a description regarding rehabilitation therapies. Specify acceptable rehabilitation therapies and the procedure for collecting rehabilitation therapy related information.
- Add a description regarding vital sign measurement in a sitting position. Add an instruction for vital sign measurement when the measurement in a semi-recumbent position was difficult.

5.1.2. **Study Results**

Compliance with Good Clinical Practices

No GCP noncompliance issues were identified by monitoring or audit.

Financial Disclosure

Financial disclosure for the study is included in Module 1 (m1.3.4)

Table 5 Patient Disposition

	GSK 1358820 240 U (N=63) N(%)	GSK1358820 400 U (N=61) N(%)	Total (N=124) N(%)
Subject status			
Completed	57 (90)	56 (92)	113 (91)
Withdrawn	6 (10)	5 (8)	11 (9)
Primary reason for Study Withdrawal			
Adverse event	0	3 (5)	3 (2)
Protocol deviation	0	0	0
Subject reached protocol-defined stopping criteria	1 (2)	0	1 (<1)
Study closed/terminated	0	0	0
Lost to follow-up	0	0	0
Investigator discretion	0	0	0
Withdrew consent	5 (8)	2 (3)	7 (6)
Investigator site closed	0	0	0

Source: Clinical Reviewer

Table 6 Protocol Violations/Deviations

Category	GSK 1358820 240 U (N=63) N(%)	GSK1358820 400 U (N=61) N(%)	Total (N=124) N(%)
ANY IMPORTANT PROTOCOL DEVIATIONS	11 (17)	12 (20)	23 (19)

Eligibility criteria not met	2 (3)	1 (2)	3 (2)
Not withdrawn after developing withdrawal criteria	1 (2)	0	1 (<1)
Excluded medication, vaccine or device	5 (8)	5 (8)	10 (8)
Visit completion	1 (2)	2 (3)	3 (2)
Assessment time point completion	1 (2)	0	1 (<1)
Wrong study treatment/administration/dose	1 (2)	2 (3)	3 (2)
Failure to report safety events per protocol	1 (2)	3 (5)	4 (3)

Source: Clinical Reviewer

REVIEWER COMMENT:

Patient disposition was similar between treatment groups, with a greater number of subjects withdrawing consent due to adverse events in the BOTOX 400 U cohort versus BOTOX 240 U cohort (3 versus 0), while overall withdrawal was higher in the BOTOX 240 U cohort versus the BOTOX 400 U cohort (6 versus 5.)

Protocol deviations were similar between treatment groups.

Table of Demographic Characteristics

Table 7

Demographic characteristics of the primary efficacy analysis

Demographic Parameters	Treatment Group		
	BOTOX 240 U (N=63) N(%)	BOTOX 400 U (N=61) N(%)	**Total** (N=124) N(%)
Sex			
Male	53 (84)	46 (75)	99 (80)
Female	10 (16)	15 (25)	25 (20)
Age			
Mean years (SD)	57.3 (10.98)	57.1 (9.90)	57.2 (10.42)
Median (years)	58.0	56.0	57.0
Min, max (years)	21, 79	29, 73	21, 79

Age Group			
< 18 years	0	0	0
≥ 18 - < 65 years	46 (73)	45 (74)	91 (73)
≥ 65 years	17 (27)	16 (26)	33 (27)
Race			
Asian- Japanese Heritage	**63 (100)**	**60 (98)**	**123 (>99)**
Mixed Race	**0**	**1 (2)**	**1 (<1)**
Ethnicity			
Hispanic or Latino	**0**	**0**	**0**
Not Hispanic or Latino	**63 (100)**	**61 (100)**	**124 (100)**
Region			
United States	**0**	**0**	**0**
Rest of the World			
Canada			
South America			
Europe			
Asia	**63 (100)**	**61 (100)**	**124 (100)**
Africa			

Source: Clinical Reviewer

REVIEWER COMMENT:

Demographics were similar between treatment groups.

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Efficacy Results – Primary Endpoint

The results of the primary efficacy endpoint, MAS responder proportion, is presented in the table below:

Table 8 Analysis Results of MAS responder proportion

Treatment	N	Responder/n (%)	Difference from 240 U (%)	95% CI (%)
GSK1358820 240 U	63	32/63 (50.8%)	18.1	(1.1, 35.0)
GSK1358820 400 U	61	42/61 (68.9%)		

Source: Statistical Reviewer

REVIEWER COMMENT:
The responder rate on the MAS score reduction in the elbow flexors at Week 6 after the first treatment was higher in the BOTOX (GSK1358820) 400 units group (68.9%, 42/61 subjects) than in the BOTOX (GSK1358820) 240 units group (50.8%, 32/63 subjects). The difference between the treatment groups was 18.1% (95% CI, 1.1 to 35.0)

Efficacy Results – Secondary and other relevant endpoints

The results of the MAS score at the elbow flexors is presented in the table below.

Table 9 Analysis Results of MAS Score in Elbow Flexors

Joint Visit	GSK1358820 240 U			GSK1358820 400 U			Difference from 240 U[1]	95% CI for Treatment Difference
	N (n)	Adjusted Mean	S.E. of Adjusted Mean	N (n)	Adjusted Mean	S.E. of Adjusted Mean		
Spasticity Gr-Elbow Flexion								
PERIOD 1 - V2 (Week 2)	63 (63)	-0.59	0.089	61 (60)	-1.07	0.102	-0.48	(-0.75, -0.22)
PERIOD 1 - V3 (Week 4)	63 (63)	-0.7	0.097	61 (59)	-1.12	0.110	-0.42	(-0.71, -0.13)
PERIOD 1 - V4 (Week 6)	63 (63)	-0.71	0.107	61 (59)	-1.09	0.128	-0.37	(-0.71, -0.04)
PERIOD 1 - V5 (Week 12)	63 (60)	-0.35	0.072	61 (57)	-0.61	0.101	-0.27	(-0.51, -0.02)

Source: Statistical Reviewer

REVIEWER COMMENT:

The analysis results of the change from baseline in MAS scores in elbow flexors are presented in the table below. The nominal p values for testing the treatment difference at Weeks 2, 4, 6 and 12 were 0.0005, 0.0048, 0.027, and 0.0329 respectively.

Additional Analyses Conducted on the Individual Trial

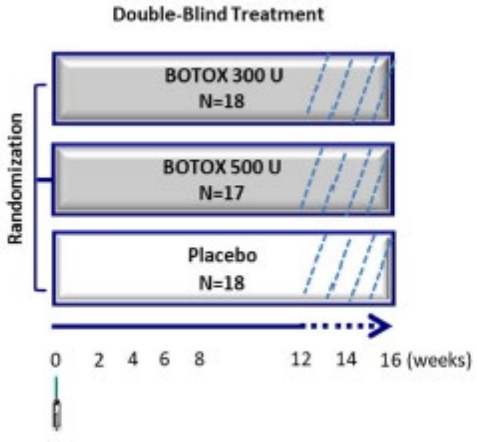
Please refer to Statistical Review (Xiangmin Zhang, July 9, 2021) for subgroup analyses.

Study 191622-127 BOTOX Treatment in Adult Patients with Upper Limb Spasticity

Study Design

The trial design is outlined in the figure below.

Figure 2 Study Design of 191622-127



Source: Sponsor

Overview and Objective

This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, single treatment cycle study conducted at 16 sites in the US and Canada. Patients received 1 fixed-dose, fixed-muscle treatment of either BOTOX 300 U (150 U elbow; 150 U shoulder), BOTOX 500 U (250 U elbow; 250 U shoulder), or placebo, as intramuscular injections divided across

defined muscles of the elbow and shoulder in a single limb. The same injection volume was used for each muscle irrespective of treatment and dose group assignment, and the dose for each muscle was evenly distributed across the number of injection sites specified for each muscle, with a maximum dose of 50 U (1 mL) per injection site. Patients were randomized to BOTOX 300 U, 500 U, or placebo in a 1:1:1 ratio, stratified by baseline spasticity (Modified Ashworth Scale-Bohannon [MAS-B] elbow flexors score = 3 or 4, and MAS-B shoulder adductors score = 3 or 4).

Dosing

Table 10 Study 191622-127: Doses and Muscles for Injection

Joint	Required Muscle	BOTOX 300 U Dose	BOTOX 500 U Dose	Number of Injection Sites/Muscle
Elbow	Biceps brachii	60 U	100 U	3
	Brachialis	30 U	50 U	2
	Brachioradialis	45 U	75 U	2
	Pronator teres	15 U	25 U	1
	Total Elbow	150 U	250 U	-
Shoulder	Pectoralis major	75 U	125 U	3
	Teres major	30 U	50 U	2
	Latissimus dorsi	45 U	75 U	3
	Total Shoulder	150 U	250 U	-

Source: Module 5.3.5.1, Protocol 191622-127, Table 2

Source: Sponsor

Study Endpoints:

Primary endpoint:

- MAS-B of the elbow flexors

Secondary Endpoints:

- MAS-B shoulder adductors
- CGI by Physician- Shoulder Specific
- Pain scale- 11-point numeric rating scale (NRS)

- Disability Assessment Scale (DAS)
- Spasticity Impact Assessment-Upper Limb (SIA-UL)

Other Measures:

- CGI by Physician
- MAS-B of the shoulder internal rotators
- CGI by Patient
- DAS: each individual domain
- SIA-UL summary scores
- Patient reported onset of spasticity symptom relief
- Patient reported benefit of injection
- Time to qualification for exit
- EurQoL-5 Dimension Self-report Questionnaire
- 12-item Short Form Health Survey

Statistical Analysis Plan:

Per protocol

The primary efficacy endpoint is the change from baseline in the MAS-B elbow flexors at week 6. Comparisons between treatment groups will be conducted by analysis of covariance (ANCOVA) with treatment group (individual BOTOX dose versus placebo) and study center as factors, and baseline MAS-B of the elbow flexors (3 or 4) as a covariate.

Continuous secondary and other efficacy variables will be summarized by treatment group and analyzed by ANCOVA or nonparametric methods, as appropriate. Categorical efficacy variables will be analyzed by chi-square test, Fisher's exact test, or logistic regression, as appropriate. All tests will be 2-sided with a significance level of 0.05. Safety variables, such as adverse event incidence rate as well as change from baseline in vital signs and laboratory tests, will be summarized by treatment group.

Protocol Amendments:

The original protocol was approved in February 2014 and amended in April 2014 (Amendment 1) and July 2014 (Amendment 2). Below is a list of the significant changes introduced in each amendment.

Amendment 1

• Prior to enrollment being initiated, the pectoralis minor muscle was removed from the injection paradigm, and its associated dose and volume were reallocated to the pectoralis

major muscle.

Amendment 2

• Retreatment was removed as an option, due to the decision not to progress with the long-term Study 191622-129. Patients who fulfilled exit criteria instead had to exit Study191622-127 from Week 12 onwards, and all patients had to exit by the Week 16 visit.

• Planned EU study sites were eliminated from the study, leaving US and Canadian sites only. This study was terminated prematurely by Allergan for administrative reasons.

Compliance with Good Clinical Practices

No GCP noncompliance issues were identified by monitoring or audit.

Financial Disclosure

Financial disclosure for the study is included in Module 1 (m1.3.4)

Patient Disposition

Fifty-three patients entered this study before it was discontinued prematurely. All 53 completed the study, including 17 who received BOTOX 500 U, 18 who received BOTOX 300 U, and 18 who received placebo.

Protocol Violations/Deviations

There were no protocol violations or deviations prior to early termination of the study.

The demographic characteristics are outlined in the table below.

Table 11 Demographic Characteristics

Demographic Parameters	Treatment Group			
	BOTOX 500 U (N=17) N(%)	BOTOX 300 U (N=18) N(%)	Placebo (N=18)	**Total** (N=53) N(%)
Sex				
Male	13(76.5)	10 (55.6)	8 (44.4)	31 (58.5)
Female	4 (23.5)	8 (44.4)	10 (55.6)	22 (21.5)
Age				
Mean years (SD)	58.8 (11.46)	59.7 (10.36)	56.2 (8.30)	58.2 (10.01)

Median (years)	62	60	55	58
Min, max (years)	25, 75	40, 77	43,73	25, 77
Age Group				
< 18 years	0	0	0	0
≥ 18 - < 65 years	12(70.6)	14 (77.8)	15 (83.3)	41 (77.4)
≥ 65 years	5 (29.4)	4(22.2)	3 (16.7)	12 (22.6)
Race				
Caucasian	11 (64.7)	13 (72.2)	9 (50)	33 (62.3)
Black	3 (17.6)	2 (11.1)	7 (38.9)	12 (22.6)
Asian	0	1 (5.6)	0	1 (1.9)
Hispanic	3 (17.6)	2 (11.1)	1 (5.6)	6 (11.3)
Other	0	0	1 (5.6)	1 (1.9)
Ethnicity				
Caucasian	11 (64.7)	13 (72.2)	9 (50)	33 (62.3)
Non-Caucasian	6 (35.3)	5 (27.8)	9 (50)	20 (37.7)

Source: Clinical Reviewer

REVIEWER COMMENT:

The demographic characteristics were similar across treatment groups except for gender and ethnicity. BOTOX 500 U cohort had greater percentage of males than females (76 % versus 24%), while BOTOX 300 U cohort and placebo cohort were more evenly distributed by gender. A greater number of Caucasians were enrolled BOTOX 500 U and BOTOX 300 U cohorts, while it was evenly distributed between Caucasians and Non-Caucasians in the placebo cohort.

Efficacy Results – Primary Endpoint

The results of the primary endpoint analysis are presented in the table below.

Table 12 Efficacy Results- Primary Endpoint

Visit	Statistics	BOTOX 500 U (N=17)	BOTOX 300 U (N=18)	Placebo (N=18)	BOTOX 500 U vs. Placebo P-value Difference 95% CI[a]	BOTOX 300 U vs. Placebo P-value Difference 95% CI[a]
Baseline	N	17	18	18		
	Mean	4.12	4.06	4.17		
	SD	0.332	0.236	0.383		
	Median	4.00	4.00	4.00		
	Min, Max	4.0, 5.0	4.0, 5.0	4.0, 5.0		
Week 6	N	16	18	17	0.048	0.094
	LS Mean[a]	-1.62	-1.47	-0.74	-0.88	-0.73
	Mean	-1.63	-1.44	-0.76	(-1.75, -0.01)	(-1.58, 0.13)
	SD	1.455	1.247	0.970		
	Median	-1.00	-1.00	0.00		
	Min, Max	-4.0, 0	-3.0, 0	-3.0, 0		

Source: Sponsor

The SAP did not prespecify how to handle missing data. Therefore, two subjects in the ITT population were not included in the above analysis because they did not have Week 6 measurements. In a post-hoc exploratory analysis that imputed the missing Week 6 measurements using last available measurements, the Applicant reported results similar to the primary analysis result: the LS mean Botox 500 U-placebo difference was -1.06 (nominal p-value=0.017, 95% CI=(-1.92, -0.20)); the LS mean Botox 300 U-placebo difference was -0.76 (nominal p value= 0.080, 95% CI=(-1.62, 0.09)).

REVIEWER COMMENT:

There was no multiplicity procedure included in the statistical analysis plan. The least squares (LS) mean Botox 500 U-placebo difference was -0.88 (nominal p-value=0.048, 95% CI=(-1.75, -0.01)); the LS mean Botox 300 U-placebo difference was -0.73 (nominal p-value=0.094, 95% CI=(-1.58, 0.13)). The directions of the estimated Botox-placebo differences favored Botox. The responder rates were 75.5% (12/16), 72.2% (13/18) and 47.1% (8/17) for the Botox 500 U group, Botox 300 U group, and placebo group, respectively. Both Botox groups had higher responder rates than the placebo group. Nominal p-values for the Botox-placebo comparisons using the chi-square test were 0.101 and 0.129 for the Botox 500 U group and Botox 300 U group, respectively.

The table below provides a summary of the main efficacy results of Study 191622-127 and Study GSK-207660.

Table 13 Summary Analysis Results of the Two Studies (Study 191622-127, Study GSK-207660)

	Study 191622-127		**Study GSK-207660**
	Botox 250 U	**Botox 150 U**	**Botox 160 U**
Change from Baseline in MAS Scores in Elbow Flexors at Week 6			
Est. Botox-Placebo Diff	-0.88	-0.73	-0.37
95% CI for Est. Diff	(-1.75, -0.01)	(-1.58, 0.13)	(-0.71, -0.04)
Nominal p-value	**0.048**	0.094	**0.027**
Responder Proportion at Week 6			
Botox-Placebo Diff	27.9%	25.2%	18.1%
95% CI for Diff	--	--	(1.1%, 35.0%)
Nominal p-value	0.101	0.129	--

Source: Statistical Reviewer

REVIEWER COMMENT:

The collective evidence from the two studies supports the addition of efficacy information of Botox for adult upper limb spasticity in the drug label for brachialis, brachioradialis and pronator teres. In Study GSK 207660, there was a statistically significant difference in treatment effect as measured by mAS responder analysis for the addition of brachialis and brachioradialis to labeling. Although study 191622-127 was terminated early, there was a nominally significant treatment effect as measured by change in mAS, for the addition of the brachialis, brachioradialis and pronator teres.

Additional Muscles:

Pronator Quadratus, Flexor Pollicis brevis/Opponens pollicis, Lumbricals/interossei

Study 191622-057: A Phase 2, multicenter, double-blind, randomized, placebo-controlled study with up to 2 treatment cycles of placebo or BOTOX (BLA 103000/eCTD SN0023, submitted 20 August 2008).

This was a Phase 2, multicenter, double-blind, randomized, placebo-controlled clinical study conducted in the US and EU comparing BOTOX to placebo for the treatment of upper limb spasticity due to upper motor neuron syndrome in patients with compromised baseline respiratory status.

The study objective was to evaluate the pulmonary function and safety of patients with stable compromised baseline respiratory status who received repeat treatment with BOTOX for focal upper limb spasticity.

Table 14 Study 191622-057: Protocol-Specified Dosing Recommendations

Clinical Pattern	Potential Muscles Involved	Recommended starting dose / U	Dose Range (U / Muscle)	Number of Injection sites
Flexed elbow	Brachioradialis	60	25-100	1-3
	Biceps	100	50-200	2-4
	Brachialis	60	40-100	2
Pronated forearm	Pronator quadratus	25	10-50	1
	Pronator teres	40	25-75	1-2
Flexed wrist	Flexor carpi radialis	50	25-100	2
	Flexor carpi ulnaris	50	20-70	2
Thumb in palm	Flexor pollicis longus	20	10-30	1

	Adductor pollicis	20	5-25	1
	Flexor pollicis brevis/ Opponens	10	5-25	1
Clenched Fist	Flexor digitorum superficialis	50	20-50	1
	Flexor digitorum profundus	50	20-50	1
Intrinsic Plus Hand	Lumbricals/interossei	10	5-10	1

Source: Sponsor

AS (elbow, wrist, fingers)

Ashworth scores were analyzed as an aggregate of scores across all muscles of the upper limb (i.e., elbow, wrist, fingers, and thumb) as well as the individual scores for each muscle (elbow, wrist, fingers, and thumb). The aggregate upper limb score was analyzed for the average score across all muscles (i.e., elbow, wrist, fingers, and thumb) within the upper limb as well as for the maximum score (worst score) across all muscles within the upper limb. Analyses of the individual muscles were based on the actual Ashworth scores.

The change from baseline in Ashworth score was calculated at each visit (weeks 1, 6, 12, 18, 24, and 30). Change scores were summarized by treatment group using mean, median, range, and standard deviation. The primary analysis testing the null hypothesis of no pairwise treatment differences between placebo and each BOTOX® group was conducted using a Wilcoxon rank sum test. For within-group analyses, the Wilcoxon signed rank test was used. Missing data were imputed using the change rate method, which takes a patient's previous observation and adjusts it according to the changes in means across all treatment groups from that visit to the missing visit.

Study AGN/HO/SPA/001-191622 (BOTOX Economic Spasticity Trial [BEST]): A Phase 3b, multicenter, randomized, placebo-controlled study of placebo or BOTOX combined with standard of care (SC), followed by an OL extension (BLA 103000/eCTD SN0157 submitted 30 March 2012).

This Phase 3, prospective, double-blind, randomized, placebo-controlled study conducted in the EU and Canada that evaluated the effectiveness of BOTOX + SC versus placebo + SC for the treatment of adult post-stroke focal spasticity as measured by the number of patients in each group who achieve their principal active functional goal as assessed by the physician.

The primary efficacy variable was the attainment of the principal active functional goal as assessed by the physician at 10 weeks post second injection (or Week 24 if no second injection

was given).

REPAS, **Resistance to Passive Movement Scale** was assessed as a secondary endpoint.

For wrist joint muscles, at 12 weeks post first injection and at 10 weeks post-second injection, there was a statistically significant greater reduction from baseline in REPAS scores of wrist extension in the BOTOX treatment group as compared to the Placebo treatment group (p=0.035 and p=0.019, respectively). For elbow joint muscles, at 12 weeks post first injection and at 10 weeks post-second injection, there was a statistically significant greater reduction from baseline in REPAS scores of elbow extension in the BOTOX treatment group as compared to the Placebo treatment group (p=0.015 and p<0.001, respectively).

Table 15 Study BEST: Protocol-Specified Dosing Recommendations

Anatomical Location	Muscle	Minimum Total Dose Units/Visit; Number of Injection Sites
Shoulder	Pectoralis major	60 units; 2-3 sites
	Latissimus dorsi	50 units; 2 sites
Elbow	Brachial Biceps (Biceps Brachii)	60 units; up to 4 sites
	Brachialis	40 units; 2 sites
	Brachioradialis	40 units; 2 sites
Wrist	Flexor Carpi Radialis	40 units; 1 to 2 sites
	Flexor Carpi Ulnaris	30 units; 1 to 2 sites
	Pronator teres	30 units; 1 to 2 sites
Fingers	Flexor Digitorum Sublimis / Flexor Digitorum Superficialis (per fascicle)	15 units; 1 to 2 sites
	Flexor Digitorum Profundus	30 units; 1 to 2 sites
	Flexor Pollicis Longus	20 units; 1 to 2 sites
	Lumbricales (per finger)	10 units
	Adductor Pollicis	10 units; 1 to 2 sites
	Opponens Pollicis	10 units; 1 to 2 sites
Hip	Hip Adductor	50 units; 2 to 4 sites
	Ileopsoas	100 units; 2-4 sites
Knee	Hamstrings	100 units; 2 to 4 sites*
	Rectus Femoris	75 units; up to 3 sites
	Total quadriceps	100 units; 2 to 4 sites

Source: Sponsor

Study 191622-056: A Phase 2, multicenter, OL study of the safety of repeated treatments of BOTOX for the treatment of focal upper limb poststroke spasticity (BLA 103000/eCTD SN0023), and the Phase 4 study, **GMA-BTX-SP-12-001 (ASPIRE)**, were included in the sponsor's submission. However, the data, open-label and real world, are not considered supportive of efficacy.

The dosing for the additional muscles across studies is outlined in the table below.

Table 16 Doses by Muscle in Legacy Studies Supporting Additional Muscles

	191622-057		BEST		191622-056	
Muscle	Protocol Dose Range[a]	Actual Doses, Median [Range]	Protocol Dose Range[a]	Actual Doses, Median [Range]	Protocol Dose Range[a]	Actual Doses, Median [Range]
Pronator quadratus	10-50 U in 1 site	17 U [7-40 U] in 1 site	-	20 U [10-25 U] in 1 site	10-50 U in 1 site	25 U [10-60 U] in 1 site
Flexor pollicis brevis/ Opponens pollicis	5-25 U in 1 site	10 U [7-75 U] in 1-2 sites	10 U in 1-2 sites	25 U [25 U] in 1-2 sites	5-25 U in 1 site	20 U [10-50 U] in 1-2 sites
Lumbricals/ Interossei	5-10 U in 1 site	23 U [7-50 U] per hand in 3 sites	10 U per finger	40 U [25-100 U] per hand	5-10 U in 1 site	40 U [10-100 U] per hand

[a] Suggested minimum total dose
Source: Brin 1997; Protocol BEST, Section 3.5.2.2, Table 2; Protocol 191622-056, Table 13.3; ISS, Tables 2-1, 2-2 and 2-3

Source: Sponsor

The exposure for the additional muscles by study is outlined in the table below.

Table 17 Summary of Sample Size (N) for the Safety Population/Exposure Period for Studies Supporting Additional Upper Limb Muscles

	DBPC[a]				Open-Label[b]		
	191622-057	BEST	Total BOTOX (DB)	Total Placebo	191622-056	GSK 207660	Total BOTOX (OL)
Pronator quadratus	24	5	29	15	28	117	145
Flexor pollicis brevis/opponens pollicis	28	0	28	15	47	117	164
Lumbricals/ Interossei	8	7	15	11	15	117	132

DBPC = double-blind, placebo-controlled; OL = open-label
[a] Patients received at least 1 injection of study medication (BOTOX or placebo).
[b] Patients received at least 1 injection of BOTOX during OL.
Source: Module 2.7.3, Section 7.2, Table 7-2, Table 7-3, and Table 7-4; Module 5.3.5.1, CSR GSK 207660, Table 3.141

Source: Sponsor

REVIEWER COMMENT:
Due to the limited number of patients injected into the additional muscles (pronator quadratus, lumbricals/interossei, flexor pollicis brevis, and opponens pollicis), statistical comparisons between treatment groups were not performed. The muscle tone change from baseline (AS and REPAS) and responder rate (= 1-point change from baseline) in the supportive studies (DBPC and OL) are presented below, by muscle (Pronator Quadratus, Flexor Pollicis Brevis/Opponens Pollicis , Lumbricals/Interossei.)

Pronator Quadratus

In Study 191622-057, the responder rate for the subgroup of patients injected in the pronator quadratus was 70% (7/10) for BOTOX 360 U, 64% (9/14) for BOTOX 240 U, and 36% (5/14) for placebo. Although no patients were treated with placebo in the pronator quadratus in Study BEST, the muscle tone (based on REPAS) change from baseline for the wrist in the BOTOX group was similar to the BOTOX treatment groups of the subgroup population in 191622-057.

Table 18 Summary of Muscle Tone Change from Baseline at Week 6 in Wrist Flexors (includes Pronator Quadratus)

			Whole Population (ITT)			Subgroup injected in pronator quadratus	
Study	Measure	Treatment Group	N	Week 6 Mean Change from Baseline	P-value vs. Placebo	N	Week 6 Mean Change from Baseline
191622-057	AS	BOTOX 240 U	52	-0.79	0.011	14	-1
		BOTOX 360 U	55	-1.19	<0.001	10	-1
		Placebo	48	-0.35	-	14	-0.4
BEST[a]	REPAS	BOTOX	63	-0.5	0.198	5	-1
		Placebo	62	-0.3	-	1	NA[c]
191622-056 (OL)[b]	AS	BOTOX ≥ 250 U	209	-0.7	-	27	-1.4
		BOTOX < 250 U	64	-0.2	-	1	-1

AS = Ashworth Scale; ITT = intent-to-treat; REPAS = resistance to passive movement scale
[a] Shows the Week 12 change from baseline, Week 6 is not available
[b] Study 191622-056 has 5 OL treatment cycles, results for Week 6 change from baseline after OL treatment cycle 1 are shown
[c] Not available – missing post-injection AS assessment
Source: Table 7-2; CSR 191622-057, Table 11-1, Listing 16.2.5-2; CSR 191622-056, Table 11.4-7, Table 14.3-3, Listing 16.2.7-3, Listing 16.2.6-1; BEST, Listing 16.2.5.1, Listing 16.2.6.12; ISE, Table 3-1

Source: Sponsor

Flexor Pollicis Brevis/Opponens Pollicis

In Study 191622-057, the responder rates for the subgroup of patients injected in the flexor pollicis brevis/opponens pollicis were 53% (8/15) for BOTOX 360 U, 69% (9/13) for BOTOX 240 U, and 33% (5/15) for placebo.

Table 19 Summary of Muscle Tone Change from Baseline at Week 6 in Thumb Spasticity (includes Flexor Pollicis Brevis/Opponens Pollicis)

			Whole Population (ITT)			Subgroup injected in flexor pollicis brevis, and/or opponens pollicis	
Study	Measure	Treatment Group	N	Week 6 Mean Change from Baseline	P-value vs. Placebo	N	Week 6 Mean Change from Baseline
191622-057	AS	BOTOX 240 U	36	-0.67	0.213	13	-1.00
		BOTOX 360 U	35	-0.63	0.285	15	-0.80
		Placebo	35	-0.35	-	15	-0.13
BEST[a]	REPAS	BOTOX	NA	NA	NA	NA	NA
		Placebo	NA	NA	NA	NA	NA
191622-056 (OL)[b]	AS	BOTOX ≥ 250 U	209	-0.6	-	40	-0.85
		BOTOX < 250 U	64	-0.3	-	7	-0.57

AS = Ashworth Scale; ITT = intent-to-treat; NA = not available; REPAS = resistance to passive movement scale
[a] Shows the Week 12 change from baseline, Week 6 is not available
[b] Study 191622-056 has 5 OL treatment cycles, results for OL treatment cycle 1 are shown
Source: Table 7-4; CSR 191622-057, Table 14.2-4, Listing 16.2.5-2, Listing 16.2.6-1; CSR 191622-056, Table 14.2-2.1, Table 14.3-3, Listing 16.2.7-3, Listing 16.2.6-1

Source: Sponsor

Lumbricals/Interossei

In Study 191622-057, the responder rates for the subgroup of patients injected in the lumbricals/interossei were 25% (1/4) for BOTOX 360 U, 50% (2/4) for BOTOX 240 U, and 33% (2/6) for placebo. In the subgroup population injected in the lumbricals/interossei, a greater improvement compared to placebo was seen in the BOTOX 240 U group, but not the BOTOX 360 U group; interpretation of the efficacy data for this subgroup is limited by the small sample size as well as an imbalance in the MAS-B baseline severity of the subgroups.

Table 20 Summary of Muscle Tone Change from Baseline at Week 6 in Finger Spasticity (includes Lumbricals/Interossei)

			Whole Population (ITT)			Subgroup injected in lumbricals/interossei	
Study	Measure	Treatment Group	N	Week 6 Mean Change from Baseline	P-value vs. Placebo	N	Week 6 Mean Change from Baseline
191622-057	AS	BOTOX 240 U	49	-0.80	0.062	4	-0.5
		BOTOX 360 U	55	-0.81	0.029	4	-0.25
		Placebo	46	-0.44	-	6	-0.33
BEST[a]	REPAS	BOTOX	63	-0.5	0.065	7	-0.14
		Placebo	62	-0.3	-	5	0.2
191622-056 (OL)[b]	AS	BOTOX ≥ 250 U	209	-1.1	-	12	-1.5
		BOTOX < 250 U	64	-0.7	-	3	-0.33

AS = Ashworth Scale; ITT = intent-to-treat; REPAS = resistance to passive movement scale
[a] Shows the Week 12 change from baseline, Week 6 was not assessed
[b] Study 191622-056 has 5 OL treatment cycles, results for OL treatment cycle 1 are shown
Source: Table 7-3; CSR 191622-057, Table 11-1, Listing 16.2.5-2, Listing 16.2.6-1; CSR 191622-056, Table 14.2-2.1, Table 14.3-3, Listing 16.2.7-3, Listing 16.2.6-1; BEST CSR, Listing 16.2.5.1, Listing 16.2.6.12; ISE, Table 3-2,

Source: Sponsor

On July 2, 2021, during labeling negotiations, the Applicant submitted additional efficacy information for lumbricals/interossei. The additional exposure data for lumbricals in double blind placebo-controlled trials is highlighted in the table below.

Table 21 Exposure for Additional Muscles by Study

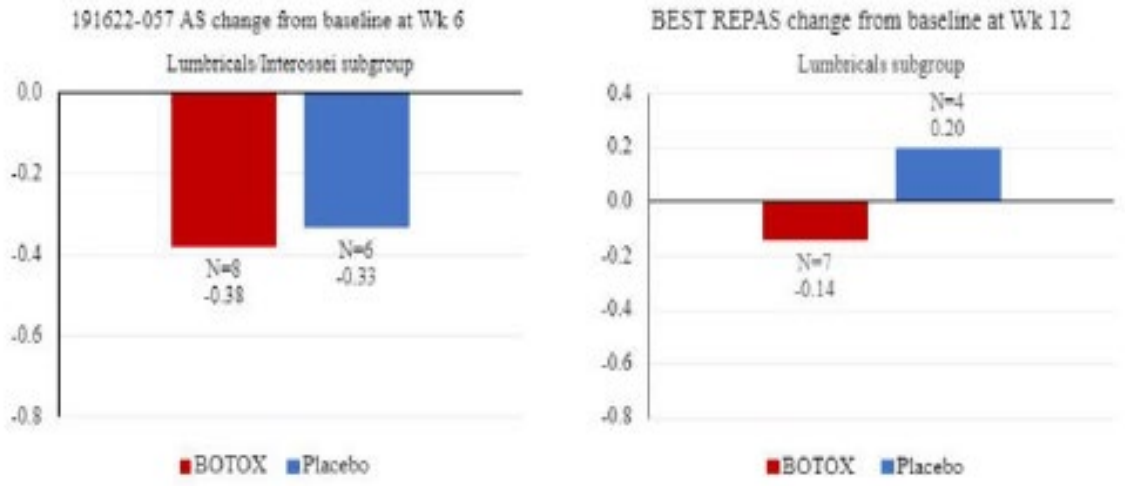
Muscle	191622-057				BEST				191622-056			GSK 207660			ASPIRE	
	N BTX	N PBO	Protocol Dose Range[a]	Actual Dose Median [Range]	N BTX	N PBO	Protocol Dose Range[a]	Actual Dose Median [Range]	N BTX	Protocol Dose Range[a]	Actual Dose Median [Range]	N BTX	Protocol Dose Range[a]	Actual Dose Median (range)	N BTX	Actual dose[a] Median
Flexor pollicis brevis/ Opponens pollicis	28	15	5-25 U in 1 site	10 U [7-75 U] in 1-2 sites	n/a	n/a	n/a	n/a	47	5-25 U in 1 site	20 U [10-50 U] in 1-2 sites	7[b]	5 to 25 U in 1 site	20-22.5 U[c] (20-50)	49[d]	25.0 U
Lumbricals/ Interossei	8	6	5-10 U in 1 site	23 U [7-50 U] per hand in 3 sites	7	4	10 U per site	40 U [25-100 U] per hand	15	5-10 U in 1 site	40 U [10-100 U] per hand	22[b]	10-50 U per hand in 3 sites	30.0-40.0 U[c] (20-100)	115	40.0 U

BTX=BOTOX; PBO=placebo
a Brin 1997; Protocol BEST, Section 3.5.2.2, Table 2; Protocol 191622-056, Table 13.3; ISS, Tables 2-1, 2-2 and 2-3; Module 5.3.5.1, CSR GSK, Table 4; ASPIRE Table 3.3.5B (LT); Table 3.3.7B (FPB)
b N treated in GSK 207660 based on Study Publication Abo 2020
c in GSK 207660, only opponens pollicis injected with median dose ranging from 20 to 22.5 U across OL cycles; lumbricals injected with median doses ranged from 30.0 to 40.0 U across OL cycles (CSR GSK 207660 Table 1.21).
d flexor pollicis brevis only

Source: Sponsor

The Applicant also submitted post hoc analyses presented graphically, for efficacy in the lumbricals for double-blind studies 191622-057 (change in Ashworth from Baseline to Week 6) and BEST (change in REPAS from Baseline to Week 12.)

Figure 3



Source: Sponsor

Post hoc analyses from an additional 22 subjects injected in finger muscles in Study GSK207660, were presented in a paper by Abo et al. The responder analysis for MAS, week 6 (primary endpoint), the proportion of patients with>1-point reduction in the MAS score was:

elbow was 68.9% (42/61) in the 400 U group and 50.8% (32/63) in the 240 U group.

wrist (68.9% for the 400 U group; 81.0% for the 240 U group),

fingers (72.1% for the 400 U group; 81.0% for the 240 U group), and

thumb (66.7% for the 400 U group; 68.3% for the 240 U group)

REVIEWER COMMENT:

Legacy studies 191622-057, BEST, are supportive of the additional muscles of the wrist/forearm and thumb; the pronator quadratus with a dose of 10-50 U BOTOX, and the flexor pollicis brevis and opponens pollicis with a dose of 5 - 25 U BOTOX, and lumbricals/interossei with a dose of 5-10 U. The muscle tone improvements in the subgroup of patients injected in these additional muscles were consistent with that observed in the ITT

population and comparable with the treatment effect seen in the approved studies (Study 1 to 5 in BOTOX USPI). In addition, the proportion of patients with ≥ 1-grade reduction in MAS-B from baseline, noted to be clinically meaningful (pre BLA meeting June 4, 2020) was numerically greater in the BOTOX treatment groups compared to placebo.

6. Review of Safety

6.1. Safety Review Approach

BOTOX is approved for the treatment of upper limb spasticity to maximum dose of 400 U (BLA 103000/5282, approved 17 April 2015).

The safety analyses presented in this review are based on the individual study reports for GSK 207660 and 191622-127.

For elbow flexor expansion, the safety results from 2 studies are presented:

- For Study GSK 207660:
    - during the double-blind phase, data are summarized for each of the BOTOX dose groups.
    - In the open-label phase, data are summarized for each BOTOX dose group and by all BOTOX dose groups combined (hereafter referred to as the 'All BOTOX' group).
    - Adverse events are presented across all treatment cycles and by treatment cycle.
- For Study 191622-127, safety analyses are presented by individual BOTOX dose group and placebo, and by all BOTOX doses combined in an 'All BOTOX' group.

6.2. Review of the Safety Database

6.2.1. Exposure

The exposure for each muscle, across studies is included in the table below.

Table 22 Summary of BOTOX Dosing (Exposure) in Clinical Studies Supporting Additional Upper Limb Muscle Labeling

Joint	Number of Participants With at Least 1 Treatment of BOTOX in Upper Limb Muscles in Double-blind, Placebo- controlled Clinical Studies and Doses of BOTOX per Muscle							Total BOTOX Open-Label[e]
	Muscle	GSK 207660[a]	191622-127[b]	BEST[c,f]	191622-057[d,f]	**Total BOTOX DBPC**	Placebo	
Elbow/ Forearm	Brachialis	61 (45 U in 1 site)	35 (30 or 50 U in 2 sites)	--	--	**96**	80	**117**
	Brachioradialis	61 (45 U in 1 site)	35 (45 or 75 U in 2 sites)	--	--	**96**	80	**117**
	Pronator teres	--	35 (15 or 25 U in 1 site)	--	--	**35**	17	**117**
	Pronator quadratus	--	--	5 (20 U [10-25 U] in 1 site)	24 (17 U [7-40 U] in 1 site)	**29**	15	**145**
Thumb/ Fingers	Flexor pollicis brevis/opponens pollicis	--	--	0 (25 U [25 U] in 1-2 sites)	28[g] (10 U [7-75 U] in 1-2 sites)	**28**	15	**164**
	Lumbricals / Interossei	--	--	7 (40 U [25-100 U] per finger)	8 (23 U [7-50 U] per hand in 3 sites)	**15**	11	**132**

DBPC = double-blind, placebo-controlled

[a] GSK 207660 is displayed for completeness; this study is the basis of proposed sBLA to expand existing upper limb spasticity label to include elbow flexors

[b] Study 191622-127 was presented to the FDA on 18 October 2016 (Seq 0237); study was prematurely discontinued for business reasons and is a supporting study for the proposed sBLA to expand existing upper limb label to include elbow flexors

[c] BEST (AGN/HO/SPA/001-191622) was included in the sBLA for thumb flexors approved in 2015

[d] Study 191622-057 was included in the original upper limb spasticity sBLA approved on 09 March 2010

[e] For the brachialis, brachioradialis, and pronator teres, open-label treatment data from Study GSK 207660; for the pronator quadratus, flexor pollicis brevis/opponens pollicis, and lumbricals/interossei, open-label treatment data from Studies 191622-056 and GSK 207660; includes participants who may have also received BOTOX in DBPC phase.

[f] Dosing was individualized to the patient per investigator judgement; the median dose [dose range] is listed here.

[g] Study 191622-057 injected opponens pollicis and/or flexor pollicis brevis.

Source: Module 2.7.3, Table 3-7, Table 3-9, and Table 3-11; Module 5.3.5.1, Protocol 191622-127, Table 2, CSR 191622-127, Section 12.1; CSR GSK 207660, Table 3.141; ISS, Table 2-1 and Table 2-2.

Source: Sponsor

The exposure by treatment cycle for Study GSK207660 is presented in the table below.

Study GSK207660

Table 23 Summary of Exposure to Study Treatment (Safety1 Population)

Injection count	BOTOX 240 U (N=63) n (%)	BOTOX 400 U (N=61) n (%)
n	63	61
1	3 (5)	4 (7)
2	5 (8)	1 (2)
3	12 (19)	16 (26)
4	43 (68)	40 (66)

Data Source: 207660 (Final) Table 3.140
Note: GSK1358820 400 units were administered to all the subjects in the Open-label phase.

Source: Sponsor

Study 191622-127

The study was terminated early due to administrative reasons; therefore, all subjects received only one injection (treatment) cycle.

6.2.2. Routine Clinical Tests

There were no clinically significant changes in hematology or clinical chemistry variables.

6.3. Safety Results

6.3.1. Deaths

In Study GSK 207660, 1 patient in the BOTOX 400 U group died from pneumonia during the double-blind phase (GSK207660- (b) (6) The event developed 69 days after the first treatment and was assessed as unrelated to study treatment by the investigator.

Listing of Fatal Serious Adverse Events (Safety1 Population)

Centre ID/ Subject ID	Age (YEARS)/ Sex/ Race / Weight (kg)	Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Date of Resolution / Duration	Time Since 1st Dose/ Time Since Last Dose/ Study Phase	Maximum Intensity/ Serious/ Withdrawal	Action Taken/ Relation to Study Treatment
Treatment: GSK1358820 400 U						
(b) (6)	54/ F/ Asian - Japanese Heritage/ 67.6	Pneumonia/ Pneumonia	Fatal/ (b) (6)	69 days/ 69 days/ Blind Phase	Severe/ Yes/ Yes	Not applicable / No

Data Source: 207660 (Final) Listing 56
MedDRA Ver. 21.1
Source: Sponsor

Case Narrative for death:

This 54-year-old female patient was enrolled in a blinded study titled A phase III study to evaluate the efficacy and safety of BOTOX in patients with post-stroke upper limb spasticity. The subject received BOTOX 400 units (intramuscular) on (b) (6) (b) (6) for poststroke upper limb spasticity.

The subject's past medical history included stroke. Concurrent medical conditions included upper limb spasticity. Additional subject notes included potentially able to bear children. Concomitant products included lansoprazole, zolpidem tartrate and miyari bacteria (Miya BM). On (b) (6) 68 days after the first dose of BOTOX 400 units, the subject developed severe - grade 3 pneumonia. The subject was treated with acetaminophen (Calonal), piperacillin hydrate +tazobactam (Tazopipe), minocycline hydrochloride, dextromethorphan hydrobromide hydrate (Medicon), levofloxacin

hydrate (Levofloxacin), clarithromycin, L-carbocisteine (Mucodyne), ambroxol hydrochloride (Mucosolvan), clenbuterol hydrochloride (Spiropent) and dchlorpheniramine maleate (Polaramine). The outcome of pneumonia was fatal on (b) (6) The reported cause of death was bacterial pneumonia. No autopsy was performed.

No deaths occurred during Study 191622-127.

REVIEWER COMMENT:
The death in study GSK207660 is not considered to be related to study treatment.

6.3.2. Serious Adverse Events

Serious adverse events from double-blind phase of Study GSK 207660 are outlined in the table below.

Table 24 Serious Adverse Events: Double-blind Phase – Study GSK 207660 (Safety Population)

System Organ Class Preferred Term	Number (%) of Patients	
	BOTOX 240 U (N=63)	BOTOX 400 U (N=61)
ANY EVENT	4 (6)	4 (7)
Nervous system disorders	2 (3)	2 (3)
Altered state of consciousness	1 (2)	0
Cerebral hemorrhage	0	1 (2)
Cerebral infarction	1 (2)	0
Dementia Alzheimer's type	0	1 (2)
Injury, poisoning and procedural complications	1 (2)	2 (3)
Ankle fracture	1 (2)	0

Pelvic fracture	0	1 (2)
Spinal compression fracture	0	1 (2)
General disorders and administration site conditions	1 (2)	1 (2)
Decreased activity	1 (2)	1 (2)
Infections and infestations	1 (2)	0
Pneumonia	1 (2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2)	0
Uterine leiomyoma	1 (2)	0
Psychiatric disorders	0	1 (2)
Delirium	0	1 (2)
Renal and urinary disorders	0	1 (2)
Dysuria	0	1 (2)

BOTOX 240 U = BOTOX 240 U in the finger, thumb and wrist flexors + placebo in the elbow flexors, BOTOX 400 U = BOTOX 240 U in the finger, thumb and wrist flexors + BOTOX 160 U in the elbow flexors (total BOTOX 400 U). MedDRA Ver. 21.1

Source Module 5.3.5.1, CSR GSK 207660, Table 43

Source: Sponsor

Serious adverse events for Study 191622-127 are outlined in the table below.

Table 25 Serious Adverse Events in Any Dose or Treatment Group – Study 191622-127 (Safety Population)

SOC PT[a]	Number (%) of Patients			
	BOTOX 500 U (N = 17)	BOTOX 300 U (N = 18)	All BOTOX (N = 35)	Placebo (N = 18)

Overall	2 (11.8%)	0 (0.0%)	2 (5.7%)	3 (16.7%)
Musculoskeletal and connective tissue disorders	1 (5.9%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Muscular weakness				
Neoplasms benign, malignant and unspecified	1 (5.9%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Prostate cancer				
Nervous system disorders				
Seizure	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (11.1%)
Transient ischaemic attack	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.6%)

[a] System organ class and PT from MedDRA Version 18.1 Source: Module 5.3.5.1, CSR 191622-127, Table 14.3-5

Source: Sponsor

REVIEWER COMMENT:

In Study GSK207660, the incidences of non-fatal SAEs that occurred between the first treatment and retreatment were 6% (4/63 subjects) in the BOTOX 240 units group and 7% (4/61 subjects) in the BOTOX 400 units group. Non-fatal SAEs occurred after 85 days were decreased activity (in the same subject who experienced pneumonia) and ankle fracture (in the same subject who experienced cerebral infarction) in the BOTOX 240 units group, delirium, dysuria, and dementia Alzheimer's type (in the same subject who experienced pelvic fracture) in the BOTOX 400 units group. The subject with the dementia of Alzheimer's type was prematurely withdrawn from the study due to diagnosis of Alzheimer's disease, at which time delirium was reported as resolving, while dysuria was ongoing. No non-fatal SAEs occurred in 2 or more subjects in either treatment group. No non-fatal SAEs were assessed as related to the study drug by the investigator.

In study 191622-127, treatment-emergent serious AEs were reported by 5 subjects in the study, including 2 in the BOTOX 500 U group (11.8%) and 3 in the placebo group. In the BOTOX 500 U group, a 72-year-old Caucasian female, reported severe muscular weakness beginning on Day 2 after treatment. The patient randomization code was unblinded by the investigator and the AE was treated with medication. The muscular weakness resolved after 148 days and was considered by the investigator to be related to study treatment.

A 68-yr-old Caucasian man who reported moderate prostate cancer beginning on Day 2 after treatment with BOTOX 500 U. The AE was reported as ongoing at study closeout on Day 116 and was considered not related to study treatment.

In the placebo group, serious AEs were 2 cases of seizure and 1 case of transient ischemic attack, all considered not related to treatment.

6.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study GSK 207660

During the double-blind phase, the rates of adverse events leading to study discontinuation were 5% (3/61) of patients in the BOTOX 400 U group and 0% (0/63) of patients in the 240 U group

The adverse events leading to study discontinuation were pneumonia, cerebral hemorrhage, and dementia Alzheimer's type. Pneumonia was a fatal adverse event, and cerebral hemorrhage and dementia Alzheimer's type were serious adverse events. None of the events were considered by
the investigator to be related to study treatment.

Study 191622-127

In Study 191622-127, no patients discontinued the study due to an adverse event.

6.3.4. Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) for Study GSK 207660 in ≥ 3% of patients, are listed in the table below.

Table 26 Adverse Events Reported in ≥ 3% of Patients in Either Treatment Group: Double-blind Phase – Study GSK 207660 (Safety Population)

	Number (%) of Patients

System Organ Class Preferred Term	BOTOX 240 U (N=63)	BOTOX 400 U (N=61)
ANY EVENT	32 (51)	34 (56)
Infections and infestations	18 (29)	13 (21)
Nasopharyngitis	11 (17)	7 (11)
Influenza	3 (5)	2 (3)
Injury, poisoning and procedural complications	5 (8)	10 (16)
Fall	3 (5)	7 (11)
Contusion	1 (2)	4 (7)
Musculoskeletal and connective tissue disorders	3 (5)	9 (15)
Arthralgia	0	3 (5)
Back pain	2 (3)	1 (2)
Muscle spasms	0	2 (3)
Investigations	4 (6)	5 (8)
Oxygen saturation decreased	2 (3)	3 (5)
Gastrointestinal disorders	4 (6)	4 (7)
Constipation	0	3 (5)
Skin and subcutaneous tissue disorders	2 (3)	4 (7)
Haemorrhage subcutaneous	0	2 (3)
Psychiatric disorders	2 (3)	3 (5)
Insomnia	1 (2)	3 (5)
Vascular disorders	3 (5)	1 (2)
Hypertension	2 (3)	1 (2)
Immune system disorders	0	2 (3)
Seasonal allergy	0	2 (3)

BOTOX 240 U = BOTOX 240 U in the finger, thumb and wrist flexors + placebo in the elbow flexors, BOTOX 400 U = BOTOX 240 U in the finger, thumb and wrist flexors + BOTOX 160 U in the elbow flexors (total BOTOX 400 U).
MedDRA Ver. 21.1
a The CSR presents percentages with 1 significant figure. Source: Module 5.3.5.1, CSR GSK 207660, Table 32

Source: Sponsor

TEAEs for study 191622-127 are presented in the table below.

Table 27 Number (%) of Patients Reporting Treatment-Emergent Adverse Events After BOTOX by Descending Incidence – Study 191622-127 (Safety Population)

Placebo Preferred Term (N=18)	BOTOX 500U (N=17)	BOTOX 300U (N=18)	All BOTOX (N=35)	
Overall	5 (29.4%)	5 (27.8%)	10 (28.6%)	9 (50.0%)
Bronchitis	1 (5.9%)	1 (5.6%)	2 (5.7%)	0
Seizure	1 (5.9%)	0	1 (2.9%)	2 (11.1%)
Muscular weakness	1 (5.9%)	0	1 (2.9%)	1 (5.6%)
Diarrhea	1 (5.9%)	0	1 (2.9%)	0
Electromyogram abnormal	1 (5.9%)	0	1 (2.9%)	0
Musculoskeletal pain	1 (5.9%)	0	1 (2.9%)	0
Nausea	1 (5.9%)	0	1 (2.9%)	0
Prostate cancer	1 (5.9%)	0	1 (2.9%)	0
Rash	1 (5.9%)	0	1 (2.9%)	0
Seasonal allergy	1 (5.9%)	0	1 (2.9%)	0
Sialoadenitis	1 (5.9%)	0	1 (2.9%)	0
Vomiting	1 (5.9%)	0	1 (2.9%)	0
Urinary tract infection	0	1 (5.6%)	1 (2.9%)	2 (11.1%)
Arthritis	0	1 (5.6%)	1 (2.9%)	0
Fall	0	1 (5.6%)	1 (2.9%)	0
Osteoarthritis	0	1 (5.6%)	1 (2.9%)	0
Tooth abscess	0	1 (5.6%)	1 (2.9%)	0
Wrist fracture	0	1 (5.6%)	1 (2.9%)	0

Source: Table 14.3-2

Source: Sponsor

REVIEWER COMMENT:

TEAEs are similar in both studies with nasopharyngitis/bronchitis, influenza being the most common in patients treated with BOTOX versus placebo.

6.3.5. **Vital Signs**

Study GSK 207660

In Study GSK 207660, vital signs (systolic and diastolic blood pressure, heart rate, and temperature) were assessed at baseline, Week 12 of Treatment Cycle 1, and Final visit at Week 48. No clinically relevant changes from baseline were observed at either assessment

Study 191622-127

In Study 191622-127, vital signs (systolic and diastolic blood pressure, pulse rate, and temperature) were assessed at baseline, Week 6, and at study exit (Week 12, 14, or 16). No clinically relevant changes from baseline were observed in vital signs during the study.

6.3.6. Electrocardiograms (ECGs)

Study GSK 207660

In Study GSK 207660, ECG assessments were performed at screening and at Visit 5/Week 12 (retreatment eligibility evaluation) of each treatment cycle.

Two patients in the BOTOX 400 U group had clinically significant abnormalities in ECG findings at screening (prior to the first treatment). These 2 patients were enrolled in this study without meeting the Exclusion Criterion "Patients with QTc > 450 msec or QTc > 480 msec in patients with bundle branch block".

One patient (2% [1/61]) in the BOTOX 400 U group whose ECG was considered abnormal (clinically significant) at screening had clinically significant abnormalities in ECG findings at Week 12 of Treatment Cycles 1, 2 and 3. However, no related adverse events were reported in this patient.

One patient (2% [1/63]) in the BOTOX 240 U group who had a normal ECG at screening had clinically significant abnormalities in ECG findings at Week 20 of Treatment Cycle 2. An adverse event of atrial fibrillation was reported in this patient; the event was assessed as mild in intensity and not related to study drug.

During the Overall study period, no other adverse events were reported as cardiac disorders.

Study 191622-127

For Study 191622-127 ECG data are not available.

6.3.7. **Immunogenicity**

Study GSK 207660

Blood samples were collected to assess immunogenicity at Screening, at V5 in the Blind phase (Week 12) and the end of study. The production of neutralizing antibodies (NaBs)was observed in 3 subjects in the BOTOX 240 units group and not in the BOTOX 400 units group. Two of the three antibody-positive subjects were positive at all time points at Screening, at Week 12 of Blind phase, and at the last visit (Week 48 or withdrawal visit). The remaining one was negative at Screening and at Week 12 of the Blind phase but was positive at withdrawal visit (after completion of Week 12 of Treatment Cycle 3).

The MAS scores at the elbow flexors at Week 6 after the treatment, as the primary endpoint in this study, for the three antibody-positive subjects were observed at least 1 decrease from baseline in and after the Treatment Cycle 2 with active treatment in elbow flexors, indicating no clear association with attenuation of efficacy due to production of NaBs.

6.4. **Analysis of Submission-Specific Safety Issues**

6.4.1.

Primary Distant Spread of Toxin (PDSOT)

Study GSK 207660

In study GSK207660, adverse events considered to be related to PDSOT are listed in the table below.

Table 28 Patient Incidence of PDSOT Adverse Events – Study GSK 207660 (Safety Population)

System Organ Class Preferred Term	Number (%) of Patients		
	Double-blind Phase		Overall Study Period[a]
	BOTOX 240 U	BOTOX 400 U	All BOTOX (N = 124)

	(N = 63)	(N = 61)	
Overall	0	5 (8)	9 (7)
Gastrointestinal disorders	0	3 (5)	7 (6)
Constipation	0	3 (5)	6 (5)
Dysphagia	0	0	1 (<1)
Eye disorders	0	1 (2)	1 (<1)
Diplopia	0	1 (2)	1 (<1)
Musculoskeletal and connective tissue disorders	0	1 (2)	1 (<1)
Muscular weakness	0	1 (2)	1 (<1)
Renal and urinary disorders	0	0	1 (<1)
Urinary retention	0	0	1 (<1)

BOTOX 240 U = BOTOX 240 U in the finger, thumb and wrist flexors + placebo in the elbow flexors,
BOTOX 400 U = BOTOX 240 U in the finger, thumb and wrist flexors + BOTOX 160 U in the elbow flexors (total BOTOX 400 U).
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[a] Includes both double-blind and open-label treatment phases Source: GSK 207660 CSR, Tables 49 and 51

Source: Sponsor

Constipation

Constipation was reported in 2.4% (3/124 subjects) of subjects in the total BOTOX group 3 subjects in the BOTOX 400 units group. For all the cases, the time to the onset of constipation from treatment ranged from 41 to 230 days after treatment.

Diplopia

Diplopia was reported in a 53-year-old male subject with a medical history of hypertension. The diplopia was reported to have an onset of 13 days after his first treatment with BOTOX 400 units. At the time of this report, the diplopia was reported as not resolved, while the subject received a subsequent BOTOX 400 units treatment without any report of PDSOT or worsening of diplopia.

Muscular Weakness

Muscular weakness was reported in a 64-year-old male subject with a medical history of depression, pain in knee, insomnia and dysuria. Muscular weakness was reported 8 days after the first treatment of BOTOX 400 units and resolved 82 days later. The muscular weakness occurred in the subject's right hand which was the same limb injected (elbow, wrist, finger and thumb flexors). The subject received the second treatment of BOTOX 400 units in the elbow,

finger, thumb and shoulder, and the third treatment of BOTOX, fingers and shoulder without any AESIs of PDSOT reported.

Study 191622-127

The single PDSOT AE preferred term reported during the study was muscular weakness. The AE was reported in 2 subjects, 1 each in the BOTOX 500 U and placebo groups.

The muscular weakness in the BOTOX group was a serious event considered by the investigator to be related to study treatment. Nineteen days before study randomization (b) (6) patient had suffered a fall which resulted in fracture of the nose and 1 finger. The patient received study treatment on (b) (6) and 2 days later the patient underwent a surgical outpatient procedure (b) (6) for the nasal fracture performed by a plastic surgeon. During this time, general anesthesia was administered, as well as lidocaine, propofol, ketorolac, ondansetron, and dexamethasone. On (b) (6) the patient arrived at the study site and reported increasing weakness and poor function in her right arm; she reported that it began the day after her study medication injection. The patient began receiving pyridostigmine on (b) (6) for the muscular weakness. She was monitored and reported an AE of electromyogram abnormal on Day 73 (b) (6) (b) (6) Both the AE of muscular weakness and electromyogram abnormal were reported as resolved on (b) (6)

The muscular weakness reported in a patient who received placebo had an onset on Day 24 was moderate in severity, and resolved after 62 days.

REVIEWER COMMENT:

The adverse events associated with PDSOT is consistent with previous studies with BOTOX and with the label.

Pulmonary Function Tests/Pulse Oximetry

Study GSK 207660

In Study GSK 207660, pulse oximetry (SpO_2) was performed at screening, Week 12 in the double-blind phase (Treatment Cycle 1) and at Final visit at Week 48.

Mean SpO_2 baseline values were similar between the treatment groups. No significant changes were noted in mean SpO_2 at Week 12 in the double-blind phase and Final visit at Week 48.

In 3 patients in the BOTOX 240 U group, post-treatment SpO_2 was decreased by 3% or more from baseline (in the double-blind phase for 1 patient and in Treatment Cycle 2 for 2 patients) and oxygen saturation decreased was reported as adverse events in these patients.
These patients remained in the study.

During the Overall study period, oxygen saturation decreased was reported at a similar frequency in the BOTOX 240 U group (8% [5/63 patients]) and the BOTOX 400 U group (5% [3/61 patients]), including the above 3 patients. All of these adverse events were mild in intensity and were unrelated to study treatment.

Study 191622-127

In Study 191622-127, pulmonary function testing was performed in 18/53 patients at select sites at baseline, Week 6 and at study exit (Week 12, 14, or 16).

Across all treatment groups, small decreases in forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were observed at post-treatment time points. In the combined BOTOX group, 33.3% of patients (4/12) had a decrease of ≥ 5% in FEV1 and 25.0% (3/12) in FVC at Week 6 vs 0% in the placebo group. At the same visit, decreases of ≥ 15% in both endpoints were seen in 16.7% (2/12) of BOTOX patients and 0% of placebo patients. By Week 12, no patients in the BOTOX group had decreases ≥ 15% vs 1 patient in the placebo group (FEV1). The adverse event of 'pulmonary function test decreased' was reported by 0% of BOTOX treated patients (0/35) and 5.6% (1/18) of placebo treated patients.

REVIEWER COMMENT:

No new safety signals associated with pulmonary function were noted.

Columbia-Suicide Severity Rating Scale

Study GSK 207660

Neither the Columbia-Suicide Severity Rating Scale (C-SSRS) nor other suicidality assessments were implemented in Study GSK 207660.

Study 191622-127

In Study 191622-127, suicidal ideation and behavior were assessed using the C-SSRS as part of the study exclusion criteria and at every study visit.

Post treatment, suicidal ideation was identified in 1 patient in the BOTOX 500 U group (5.9% [1/18]), 0 patients in the BOTOX 300 U group (0% [0/18]), and 2 patients in the placebo group (11.1% [2/18]). No suicidal behavior was recorded in any patient.

REVIEWER COMMENT:

No new safety signals associated with suicidality were noted.

6.5. Safety Analyses by Demographic Subgroups

Adverse Events by Age

Study GSK 207660

Adverse events by age for Study GSK 207660 are summarized in the table below.

Table 29 Adverse Events Occurring in ≥ 3% and More Than 1 Patient in Any Dose or Treatment Group by Age: Overall Study period –Study GSK 207660 (Safety Population)

SOC PT	Number (%) of Patients					
	19 - 64 years			≥ 65 years		
	BOTOX 240 U (N=46)	BOTOX 400 U (N=45)	Total (N=91)	BOTOX 240 U (N=17)	BOTOX 400 U (N=16)	Total (N=33)
ANY EVENT 38 (83)	34 (76)	72 (79)	14 (82)	15 (94)	29 (88)	
Blood and lymphatic system disorders Anaemia -	-	-	1 (6)	1 (6)	2 (6)	
Gastrointestinal disorders						
Dental caries 2 (4)	1 (2)	3 (3)	-	2 (13)	2 (6)	
Stomatitis -	-	-	1 (6)	1 (6)	2 (6)	
Toothache 1 (2)	-	1 (1)	1 (6)	-	1 (3)	
Constipation 1 (2)	5 (11)	6 (7)	-	-	-	
General disorders and administration site conditions						

Decreased activity -	1 (2)	1 (1)	1 (6)	-	1 (3)
Non-cardiac chest pain 1 (2)	-	1 (1)	-	1 (6)	1 (3)
Pyrexia 2 (4)	-	2 (2)	1 (6)	-	1 (3)
Immune system disorders					
Seasonal allergy 1 (2)	5 (11)	6 (7)	1 (6)	-	1 (3)
Infections and infestations					
Nasopharyngitis 11 (24)	9 (20)	20 (22)	4 (24)	1 (6)	5 (15)
Bronchitis -	-	-	2 (12)	-	2 (6)
Cystitis -	-	-	1 (6)	1 (6)	2 (6)
Gingivitis 2 (4)	-	2 (2)	-	2 (13)	2 (6)
Upper respiratory tract infection 1 (2)	1 (2)	2 (2)	1 (6)	1 (6)	2 (6)
Pneumonia -	2 (4)	2 (2)	1 (6)	-	1 (3)
Skin bacterial infection -	1 (2)	1 (1)	1 (6)	-	1 (3)
Tinea pedis 1 (2)	1 (2)	2 (2)	-	1 (6)	1 (3)
Sinusitis -	2 (4)	2 (2)	-	-	-
Influenza 3 (7)	2 (4)	5 (5)	-	-	-
Pharyngitis 2 (4)	2 (4)	4 (4)	-	-	-
Dermatophytosis of nail -	2 (4)	2 (2)	-	-	-
Injury, poisoning and procedural complications					
Fall 9 (20)	10 (22)	19 (21)	2 (12)	5 (31)	7 (21)
Contusion 6 (13)	6 (13)	12 (13)	-	3 (19)	3 (9)
Ligament sprain 2 (4)	1 (2)	3 (3)	1 (6)	-	1 (3)
Skin abrasion 1 (2)	2 (4)	3 (3)	1 (6)	-	1 (3)
Rib fracture 2 (4)	-	2 (2)	-	-	-
Investigations					
Oxygen saturation decreased 3 (7)	1 (2)	4 (4)	2 (12)	2 (13)	4 (12)
Weight increased -	1 (2)	1 (1)	1 (6)	-	1 (3)
Alanine aminotransferase increased 2 (4)	-	2 (2)	-	-	-

SOC PT	Number (%) of Patients	
	19 - 64 years	≥ 65 years

	BOTOX 240 U (N=46)	BOTOX 400 U (N=45)	Total (N=91)	BOTOX 240 U (N=17)	BOTOX 400 U (N=16)	Total (N=33)
Musculoskeletal and connective tissue disorders						
Back pain	4 (9)	2 (4)	6 (7)	2 (12)	1 (6)	3 (9)
Pain in extremity	-	1 (2)	1 (1)	1 (6)	1 (6)	2 (6)
Arthralgia	2 (4)	2 (4)	4 (4)	-	1 (6)	1 (3)
Musculoskeletal pain	2 (4)	2 (4)	4 (4)	-	1 (6)	1 (3)
Muscle spasms	-	2 (4)	2 (2)	-	-	-
Nervous system disorders						
Cerebral haemorrhage	-	1 (2)	1 (1)	-	1 (6)	1 (3)
Dizziness	-	1 (2)	1 (1)	1 (6)	-	1 (3)
Parkinsonism	-	2 (4)	2 (2)	-	-	-
Psychiatric disorders Insomnia	1 (2)	3 (7)	4 (4)	-	1 (6)	1 (3)
Renal and urinary disorders						
Dysuria	-	1 (2)	1 (1)	1 (6)	-	1 (3)
Pollakiuria	-	1 (2)	1 (1)	-	1 (6)	1 (3)
Skin and subcutaneous tissue disorders						
Haemorrhage subcutaneous	-	-	-	-	2 (13)	2 (6)
Dermatitis contact	1 (2)	-	1 (1)	-	1 (6)	1 (3)
Eczema	-	2 (4)	2 (2)	1 (6)	-	1 (3)
Erythema	1 (2)	-	1 (1)	1 (6)	-	1 (3)
Hyperkeratosis	-	2 (4)	2 (2)	-	-	-

Vascular disorders Hypertension	2 (4)	1 (2)	3 (3)	2 (12)	1 (6)	3 (9)

- = 0 (0.0%)

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Source: Module 5.3.5.1, CSR GSK 207660, Table 38

Source: Sponsor

REVIEWER COMMENT:

There were no significant differences in adverse events identified by age group.

Adverse Events by Sex

Adverse events by sex for Study GSK 207660 are summarized in the table below.

Table 30 Adverse Events Occurring in ≥ 3% and More Than 1 Patient in Any Dose or Treatment Group by Sex: Overall Study Period – Study GSK 207660 (Safety Population)

SOC PT	Number (%) of Patients					
	Male			Female		
	BOTOX 240 U (N=53)	BOTOX 400 U (N=46)	Total (N=99)	BOTOX 240 U (N=10)	BOTOX 400 U (N=15)	Total (N=25)
ANY EVENT	44 (83)	35 (76)	79 (80)	8 (80)	14 (93)	22 (88)
Gastrointestinal disorders						
Constipation	-	3 (7)	3 (3)	1 (10)	2 (13)	3 (12)
Dental caries	2 (4)	2 (4)	4 (4)	-	1 (7)	1 (4)
Toothache	2 (4)	-	2 (2)	-	-	-
Stomatitis	1 (2)	-	1 (1)	-	1 (7)	1 (4)
General disorders and administration site conditions						
Decreased activity	-	-	-	1 (10)	1 (7)	2 (8)
Non-cardiac chest pain	1 (2)	-	1 (1)	-	1 (7)	1 (4)
Pyrexia	3 (6)	-	3 (3)	-	-	-

Immune system disorders Seasonal allergy	2 (4)	4 (9)	6 (6)	-	1 (7)	1 (4)
Infections and infestations						
Nasopharyngitis	13 (25)	8 (17)	21 (21)	2 (20)	2 (13)	4 (16)
Influenza	1 (2)	1 (2)	2 (2)	2 (20)	1 (7)	3 (12)
Cystitis	-	-	-	1 (10)	1 (7)	2 (8)
Pneumonia	-	1 (2)	1 (1)	1 (10)	1 (7)	2 (8)
Dermatophytosis of nail	-	1 (2)	1 (1)	-	1 (7)	1 (4)
Otitis externa	1 (2)	-	1 (1)	-	1 (7)	1 (4)
Sinusitis	-	1 (2)	1 (1)	-	1 (7)	1 (4)
Skin bacterial infection	1 (2)	-	1 (1)	-	1 (7)	1 (4)
Upper respiratory tract infection	2 (4)	1 (2)	3 (3)	-	1 (7)	1 (4)
Gingivitis	2 (4)	2 (4)	4 (4)	-	-	-
Pharyngitis	2 (4)	2 (4)	4 (4)	-	-	-
Tinea pedis	1 (2)	2 (4)	3 (3)	-	-	-
Bronchitis	2 (4)	-	2 (2)	-	-	-
Injury, poisoning and procedural complications						
Fall	8 (15)	8 (17)	16 (16)	3 (30)	7 (47)	10 (40)
Contusion	5 (9)	5 (11)	10 (10)	1 (10)	4 (27)	5 (20)
Ligament sprain	2 (4)	-	2 (2)	1 (10)	1 (7)	2 (8)
Skin abrasion	1 (2)	2 (4)	3 (3)	1 (10)	-	1 (4)
Rib fracture	2 (4)	-	2 (2)	-	-	-
Investigations				-		
Oxygen saturation decreased	5 (9)	3 (7)	8 (8)	-	-	-
Alanine aminotransferase increased	2 (4)	-	2 (2)	-	-	-

	Number (%) of Patients

SOC PT	Male			Female		
	BOTOX 240 U (N=53)	BOTOX 400 U (N=46)	Total (N=99)	BOTOX 240 U (N=10)	BOTOX 400 U (N=15)	Total (N=25)
Musculoskeletal and connective tissue disorders						
Back pain	6 (11)	1 (2)	7 (7)	-	2 (13)	2 (8)
Pain in extremity	1 (2)	-	1 (1)	-	2 (13)	2 (8)
Arthralgia	2 (4)	2 (4)	4 (4)	-	1 (7)	1 (4)
Musculoskeletal pain	2 (4)	3 (7)	5 (5)	-	-	-
Muscle spasms	-	2 (4)	2 (2)	-	-	-
Nervous system disorders				-		
Cerebral haemorrhage	-	1 (2)	1 (1)	-	1 (7)	1 (4)
Parkinsonism	-	1 (2)	1 (1)	-	1 (7)	1 (4)
Psychiatric disorders Insomnia	1 (2)	1 (2)	2 (2)	-	3 (20)	3 (12)
Renal and urinary disorders						
Dysuria	1 (2)	-	1 (1)	-	1 (7)	1 (4)
Pollakiuria	-	1 (2)	1 (1)	-	1 (7)	1 (4)
Skin and subcutaneous tissue disorders						
Haemorrhage subcutaneous	-	-	-	-	2 (13)	2 (8)
Dermatitis contact	-	1 (2)	1 (1)	1 (10)	-	1 (4)
Hyperkeratosis	-	1 (2)	1 (1)	-	1 (7)	1 (4)
Eczema	1 (2)	2 (4)	3 (3)	-	-	-
Erythema	2 (4)	-	2 (2)	-	-	-

Vascular disorders						
Haematoma	-	1 (2)	1 (1)	1 (10)	-	1 (4)
Hypertension	3 (6)	2 (4)	5 (5)	1 (10)	-	1 (4)

- = 0 (0.0%)

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Source: Module 5.3.5.1, CSR GSK 207660, Table 36

Source: Sponsor

REVIEWER COMMENT:

There were more males than females with a greater percentage of females sustaining injury (falls, contusions) than males, 40% versus 16% respectively.

6.6. Safety in the Postmarket Setting

6.6.1. Safety Concerns Identified Through Postmarket Experience

During the period January 1, 1990 to May 31, 2020, the most frequently reported PTs for spasticity in adults, excluding 205 events where off-label use was entered as an event PT, were muscular weakness (310), asthenia (154), dysphagia (133), fall (114), pyrexia (102), gait disturbance (99), pain in extremity (95), drug ineffective (93), and injection site pain (87). During the period January 1, 1990 to May 31, 2020, the most frequently reported PTs for upper limb spasticity in adults, excluding 34 events where off-label use was entered as an event PT, were muscular weakness (83), asthenia (32), seizure (31), dysphagia (30), pyrexia (29), rash (29), fall (28), pneumonia (26), and pain in extremity (24).

The reported events are either consistent with the known safety profile of BOTOX or conditions commonly associated with the patient's underlying disease.

6.7. Integrated Assessment of Safety

As agreed upon with the Agency, the assessment of safety for BOTOX to provide dosing guidance in approved elbow labeling for injection of 3 additional elbow flexors (brachialis, brachioradialis, and pronator teres) is comprised of the safety data from clinical studies GSK 207660 and 191622-127. These studies have been systematically summarized in the preceding sections of this document. As the doses in the elbow flexors did not exceed 250 U, no changes are proposed for the approved maximum adult upper limb spasticity dose of 400 U.

The safety of the 400 U maximum dose was previously established for adult upper limb spasticity (BLA 103000/5282, approved April 17, 2015). In comparison, the GSK 207660 and 191622-127 studies do not provide any new safety signals, and the overall safety profile is consistent with that of the demonstrated safety of 400 U BOTOX.

7. Advisory Committee Meeting and Other External Consultations

NA

8. Labeling Recommendations

8.1. Prescription Drug Labeling

Based on the safety and efficacy results from studies, 191622-127, GSK207660 and legacy studies, 191-622-057 and BEST, I recommend the following revisions to the label:

Section 2.6 Adult Spasticity, Table 4:

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- **Table 1: BOTOX Dosing by Muscle for Adult Upper Limb Spasticity**

Muscle	Recommended Dose Total Dosage (Number of Sites)
Biceps Brachii	60 Units to 200 Units divided in 2-4 sites
Brachioradialis	45 Units to 75 Units divided in 1-2 sites
Brachialis	30 Units to 50 Units divided in 1-2 sites
Pronator Teres	15 Units to 25 Units in 1 site
Pronator Quadratus	10 Units to 50 Units in 1 site
Flexor Carpi Radialis	12.5 Units to 50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units to 50 Units in 1 site
Flexor Digitorum Profundus	30 Units to 50 Units in 1 site
Flexor Digitorum Sublimis	30 Units to 50 Units in 1 site
Lumbricals/Interossei	5 Units to 10 Units in 1 site
Adductor Pollicis	20 Units in 1 site
Flexor Pollicis Longus	20 Units in 1 site
Flexor pollicis brevis/ Opponens pollicis	5 Units to 25 Units in 1 site

Section 14.5 Adult Spasticity

Adult Upper Limb Spasticity
The efficacy of BOTOX for the treatment of adult upper limb spasticity was evaluated in several randomized, multi-center, double-blind, placebo-controlled studies (Studies 1 through 6).

Study 6 (NCT03261167) enrolled 124 post-stroke adult patients with upper limb spasticity. In Study 6, 61 patients received 160 Units BOTOX divided among 3 elbow flexors (biceps brachii, brachioradialis, and brachialis) and 63 patients received placebo (see Table 40). In Study 6, EMG, nerve stimulation, or ultrasound techniques were recommended to assist in proper muscle localization for injections. The duration of follow-up was 12 weeks in Study 6.

Table 40: BOTOX Dose and Injection Sites in Study 6

Muscles Injected	Study 6						
	BOTOX 160 U (Units)	Volume (mL)	Number of Injection Sites				
Elbow Biceps Brachii	70	1.4	2				
Brachioradialis	45	0.9	1				
Brachialis	45	0.9	1				

(b) (4) the change from baseline in elbow flexor tone measured by modified Ashworth Scale at Week 6 are presented in Table 41.

Table 41: Primary Efficacy Endpoint Results for Elbow Flexors at Week 6 in Study 6

	Study 6				
	BOTOX 160 U (N=61)	Placebo (N=63)			
Mean Change from Baseline in Elbow Flexor Muscle Tone on the modified Ashworth Scale at Week 6	-1.09*	-0.71			

* nominal p value<0.05

9. Risk Evaluation and Mitigation Strategies (REMS)

NA

10. Postmarketing Requirements and Commitments

NA

11. Appendices

11.1. References

Abo, M et al. Efficacy and Safety of OnabotulinumtoxinA 400 Units in Patients with Post-Stroke Upper Limb Spasticity: Final Report of a Randomized, Double-Blind, Placebo-Controlled Trial with an Open-Label Extension Phase. Toxins 2020, 12, 127.

11.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): GSK 207660, 191622-127,, 191622-057, AGN/HO/SPA/001-191622, 191622-056

Was a list of clinical investigators provided:		Yes ☒	No ☐ (Request list from Applicant)
	Total number of investigators identified: 6		
	Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
	Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
	If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0		

	Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0			
Is an attachment provided with details of the disclosable financial interests/arrangements:			Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:			Yes ☒	No ☐ (Request information from Applicant)
	Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6			
Is an attachment provided with the reason:			Yes ☒	No ☐ (Request explanation from Applicant)

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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/

SUSANNE R GOLDSTEIN
07/26/2021 03:57:26 PM

LAURA A JAWIDZIK
07/26/2021 04:40:17 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103000Orig1s5320

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Number:	103000 Supplement 5320
Drug Name:	Botox (onabotulinumtoxinA)
Indication:	Treatment of spasticity in patients 2 years of age and older
Applicant:	Allergan, Inc.
Dates:	Receipt date: September 28, 2020 PDUFA Goal Date: July 28, 2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader James H.M. Hung, Ph.D., Director
Medical Division:	Division of Neurology I
Clinical Team:	Susanne Goldstein, M.D., Clinical Reviewer Laura Jawidzik, M.D., Team Leader
Project Manager:	Taura Holmes, Pharm.D.

TABLE OF CONTENTS

LIST OF TABLES

1 EXECUTIVE SUMMARY

On September 28, 2020, Allergan, Inc. (the Applicant) submitted a supplemental biologics license application (sBLA) for Botox (onabotulinumtoxinA) to support the addition of dosing guidance for additional upper limb muscles within the approved muscle groups for adult upper limb spasticity. The application included two randomized, double-blind, placebo-controlled, parallel-group, clinical studies 191622-127 and GSK-207660 to support new efficacy information for the elbow flexors. Study 191622-127 had three treatment groups: Botox 500 units (U), Botox 300 U, and placebo; the actual dose received in the elbow flexors for each subject was Botox 250 U, 150 U, or placebo. Study GSK-207660 had two treatment groups: Botox 400 U and Botox 240 U; the actual dose received in the elbow flexors for each subject was Botox 240 U or placebo.

Table 1. Summary of MAS-B change from baseline at Week 6 for elbow flexors

Study	Measure	Analysis Population	Treatment Group	N	Week 6 LS Mean Change from Baseline	P-value vs. Placebo
GSK 207660	MAS-B	ITT	BOTOX 400 U	61	-1.09	< 0.05*
			BOTOX 240 U (placebo in elbow)	63	-0.71	-
191622-127	MAS-B	ITT	BOTOX 500 U	16	-1.62	0.048
			BOTOX 300 U	18	-1.47	0.094
			Placebo	17	-0.74	-

ITT = intent-to-treat; MAS-B = modified Ashworth scale-Bohannon
* Statistically significant based on 95% confidence interval of (-0.71, -0.04)

Source: Table 3-3 in the summary of clinical efficacy

Table 2. Summary of MAS-B responder rate at Week 6 for elbow flexors

Study	Measure	Analysis Population	Treatment Group	N	Responder/n (%)	Difference from Placebo	P-value vs. Placebo
GSK 207660	MAS-B	ITT	BOTOX 400 U	61	42/61 (68.9%)	18.1%	< 0.05*
			BOTOX 240 U (placebo in elbow)	63	32/63 (50.8%)	-	-
191622-127	MAS-B	ITT	BOTOX 500 U	16	12/16 (75.0%)	27.9%	0.101
			BOTOX 300 U	18	13/18 (72.2%)	25.1%	0.129
			Placebo	17	8/17 (47.1%)	-	-

ITT = intent-to-treat; MAS-B = modified Ashworth scale-Bohannon
* Statistically significant based on 95% confidence interval of (1.1, 35.0)

Source: Table 3-4 in the summary of clinical efficacy

Table 1 and **Table 2** provide the summary of the main efficacy results of the two studies. These results support the addition of efficacy information of Botox for adult upper limb spasticity in the drug label.

2 INTRODUCTION

2.1 Overview

This sBLA for Botox includes two double-blind, randomized, placebo-controlled clinical studies to support new efficacy information of Botox for the treatment of upper limb spasticity. The two studies are summarized below and reviewed in Section 3.

Table 3. Clinical studies in this review

Study	Phase and Design	Study Duration	Study Arm (Number of randomized subjects per arm)	Study Population
191622-127	Phase 3, randomized, double-blind, placebo-controlled, parallel-group	4-week screening period and 12 to16-week post-treatment follow-up	Botox 500 U (17) Botox 300 U (18) Placebo (18)	Female and male post-stroke patients with upper limb spasticity aged 18-80 years.
GSK-207660	Phase 3, randomized, double-blind, placebo-controlled, parallel-group	4-week screening period, 12-week post-treatment follow-up, and 30 week open-label period	Botox 400 U (61) Botox 240 U (63)	Female and male post-stroke patients with upper limb spasticity aged 20-80 years.

Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of the NDA is located at
\\CDSESUB1\evsprod\BLA103000\0428\

The study reports are located at
\\CDSESUB1\evsprod\BLA103000\0428\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ul-spasticity\5351-stud-rep-contr\

The datasets are located at
\\CDSESUB1\evsprod\BLA103000\0428\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

3.2 Evaluation of Efficacy

3.2.1 Study 191622-127

3.2.1.1 Design and Endpoints

Study 191622-127 was a randomized, double-blind, parallel-group, 3-arm, multi-center, Phase 3 clinical study to evaluate the efficacy, safety, and tolerability of Botox 300 U and Botox 500 U in the treatment of spasticity involving the muscles of the elbow and shoulder of adult poststroke patients. In the initial study plan, approximately 423 subjects were planned to be enrolled and 402 subjects randomized in a 1:1:1 ratio to receive Botox 500 U, Botox 300 U, or placebo. Subjects in the Botox 500 U group were planned to receive Botox 250 U into the elbow flexors (biceps brachii, brachialis, brachioradialis, and pronator teres) and Botox 250 U into the shoulder flexors (pectoralis major, teres major, and latissimus dorsi); subjects in the Botox 300 U group were planned to receive Botox 150 U into the elbow flexors and Botox 150 U into the shoulder flexors.

The study consisted of a screening period of up to 4 weeks and a double-blind placebo-controlled treatment cycle of 12 to 16 weeks. All subjects were planned to be followed up at weeks 2, 4, 6, 8, and 12 post-treatment.

The primary endpoint was the change from baseline in Modified Ashworth Scale-Bohannon (MAS-B) of the elbow flexors. The MAS-B scores of 0, 1, 1+, 2, 3, or 4 were coded as 0, 1, 2, 3, 4, or 5, respectively.

3.2.1.2 Statistical Methodologies

The efficacy analysis population was the intention-to-treat (ITT) population consisting of all randomized subjects.

The primary efficacy variable was planned to be analyzed at week 6 using an analysis of covariance (ANCOVA) model with treatment group as a factor and baseline MAS-B scores of the elbow flexors as a covariate. In addition, a responder status was determined according to whether or not a patient has at least a 1-grade reduction from baseline on the MAS-B elbow flexors at each post-treatment visit. The percentages of responders at each visit were planned to be analyzed by Pearson's chi-square test or Fisher's exact test.

3.2.1.3 Subject Disposition, Demographic and Baseline Characteristics

This study was terminated prematurely by the Applicant for administrative reasons, leading to an actual number of randomized subjects much smaller than what was planned. A total of 53 subjects in the United States and Canada entered the study. All 53 subject completed the study, among which 17 (32%) were randomized to the Botox 500 U group, 18 (34%) to the Botox 300 U group, and 18 (34%) to the placebo group.

Table 4. Study 191622-127 subject demographics, randomized population

Variable	Attribute	BOTOX 500U (N = 17)	BOTOX 300 U (N = 18)	Placebo (N = 18)	Total (N = 53)
Age (years)	N	17	18	18	53
	Mean	58.8	59.7	56.2	58.2
	SD	11.46	10.36	8.30	10.01
	Median	62.0	60.0	55.0	58.0
	Min	25	40	43	25
	Max	75	77	73	77
	< 65	12 (70.6%)	14 (77.8%)	15 (83.3%)	41 (77.4%)
	≥ 65	5 (29.4%)	4 (22.2%)	3 (16.7%)	12 (22.6%)
Sex	N	17	18	18	53
	Male	13 (76.5%)	10 (55.6%)	8 (44.4%)	31 (58.5%)
	Female	4 (23.5%)	8 (44.4%)	10 (55.6%)	22 (41.5%)
Race	N	17	18	18	53
	Caucasian	11 (64.7%)	13 (72.2%)	9 (50.0%)	33 (62.3%)
	Black	3 (17.6%)	2 (11.1%)	7 (38.9%)	12 (22.6%)
	Asian	0	1 (5.6%)	0	1 (1.9%)
	Hispanic	3 (17.6%)	2 (11.1%)	1 (5.6%)	6 (11.3%)
	Other	0	0	1 (5.6%)	1 (1.9%)
	Caucasian	11 (64.7%)	13 (72.2%)	9 (50.0%)	33 (62.3%)
	Non-Caucasian	6 (35.3%)	5 (27.8%)	9 (50.0%)	20 (37.7%)

Source: selected from Table 10-1 in the clinical study report of Study 191622-127

Table 4 summarizes the demographics of subjects in the randomized population. Based on the observations in **Table 4** and exploratory tests of independence between the treatment groups and demographic factors (not shown), the Botox and placebo groups were generally balanced in terms of sex, race, and age. The average age of all randomized subjects was 58.2 years (standard deviation (SD) = 10.01). Over 62% of the randomized population were white. There were more males (58.5%) than females (41.5%).

3.2.1.4 Results and Conclusions

Table 5. Study 191622-127 analysis of the primary endpoint, ITT population

Visit	Statistics	BOTOX 500 U (N=17)	BOTOX 300 U (N=18)	Placebo (N=18)	BOTOX 500 U vs. Placebo P-value Difference 95% CI[a]	BOTOX 300 U vs. Placebo P-value Difference 95% CI[a]
Baseline	N	17	18	18		
	Mean	4.12	4.06	4.17		
	SD	0.332	0.236	0.383		
	Median	4.00	4.00	4.00		
	Min, Max	4.0, 5.0	4.0, 5.0	4.0, 5.0		
Week 6	N	16	18	17	0.048	0.094
	LS Mean[a]	-1.62	-1.47	-0.74	-0.88	-0.73
	Mean	-1.63	-1.44	-0.76	(-1.75, -0.01)	(-1.58, 0.13)
	SD	1.455	1.247	0.970		
	Median	-1.00	-1.00	0.00		
	Min, Max	-4.0, 0	-3.0, 0	-3.0, 0		

ITT = intent to treat; MAS-B = Modified Ashworth Scale-Bohannon; Max = maximum; Min = minimum; SD = standard deviation

[a] P-value, treatment difference, 95% CI, and LS Mean (least-square mean) are based on an ANCOVA model with baseline MAS-B of the elbow flexors as a covariate. The estimated differences are based on the least-square means.

Source: selected from Table 11-1 in the clinical study report of Study 191622-127

Table 5 presents the analysis results of the primary endpoint. There was no multiplicity procedure in the statistical analysis plan (SAP). The least squares (LS) mean Botox 500 U-placebo difference was -0.88 (nominal p-value=0.048, 95% CI=(-1.75, -0.01)); the LS mean Botox 300 U-placebo difference was -0.73 (nominal p-value=0.094, 95% CI=(-1.58, 0.13)). The directions of the estimated Botox-placebo differences favored Botox.

The SAP did not prespecify how to handle missing data. Therefore, two subjects in the ITT population were not included in the above analysis because they did not have Week 6 measurements. In a post-hoc exploratory analysis that impute the missing Week 6 measurements using last available measurements, the Applicant reported results similar to the primary analysis result: the LS mean Botox 500 U-placebo difference was -1.06 (nominal p-value=0.017, 95% CI=(-1.92, -0.20)); the LS mean Botox 300 U-placebo difference was -0.76 (nominal p-value=0.080, 95% CI=(-1.62, 0.09)).

The responder rates were 75.5% (12/16), 72.2% (13/18) and 47.1% (8/17) for the Botox 500 U group, Botox 300 U group, and placebo group, respectively. Both Botox groups had higher responder rates than the placebo group. Nominal p-values for the Botox-placebo comparisons

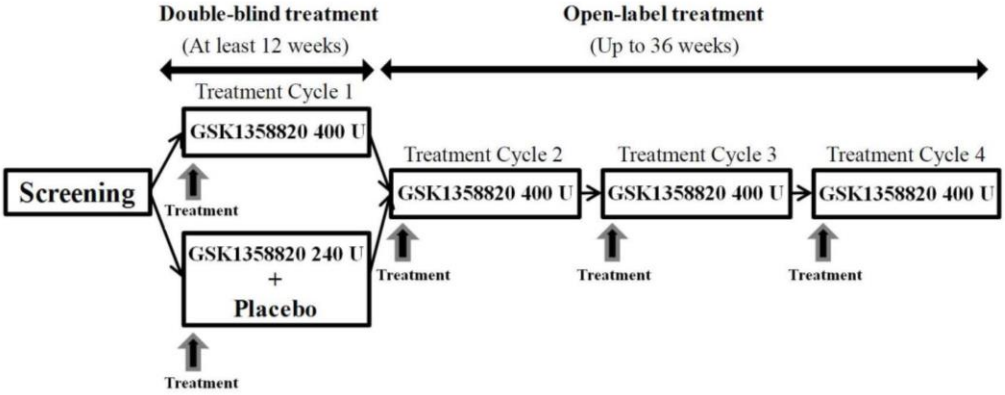
using the chi-square test were 0.101 and 0.129 for the Botox 500 U group and Botox 300 U group, respectively.

3.2.2 Study GSK-207660

3.2.2.1 Design and Endpoints

Study GSK-207660 was a randomized, double-blind, parallel-group, 2-arm, multi-center, Phase 3 clinical study to evaluate the efficacy, safety, and tolerability of Botox 400 U comparing to that of 240 U in patients with post-stroke upper limb spasticity. Approximately 120 subjects were planned to be enrolled and randomized in a 1:1 ratio to receive Botox 400 U or Botox 240 U. Subjects in the Botox 400 U group were planned to receive Botox 240 units into the finger, thumb, and wrist flexors and Botox 160 units into the elbow flexors (biceps brachii, brachioradialis, and brachialis); subjects in the Botox 240 U group were planned to receive Botox 240 units into the finger, thumb, and wrist flexors and placebo into the elbow flexors.

Figure 1. Study GSK-207660 study design



Source: Figure 1 in the clinical study report of Study GSK-207660

Figure 1 depicts the study design. The study consisted of a screening period of up to 4 weeks, a double-blind placebo-controlled treatment phase of at least 12 weeks, and an open-label period of up to 36 weeks. All subjects were planned to be followed up in a blinded fashion at weeks 2, 4, 6, and 12 post-treatment. Afterwards, eligible subjects had the option to enter the open-label period.

The primary endpoint is the proportion of subjects whose MAS score on the elbow at Week 6 of the initial dose decreased by at least 1 level from the baseline (i.e. proportion of responders). Subjects with no MAS score available at Week 6 were counted in as non-responders. The MAS scores of 0, 1, 1+, 2, 3, or 4 were coded as 0, 1, 2, 3, 4, or 5, respectively.

3.2.2.2 Statistical Methodologies

The efficacy analysis population was the modified intention-to-treat (mITT) population, defined as all subjects randomized in the study and had at least 1 post-baseline efficacy assessment.

No formal statistical hypothesis testing was planned. A 95% confidence interval for the difference in responder proportions was planned to be reported for the primary endpoint. In addition, a mixed model for repeated measurement (MMRM) was planned to analyze the change from baseline in MAS scores in elbow flexors. The model included treatment, visit, treatment-by-visit interaction, baseline MAS score, baseline-by-visit interaction. The unstructured variance structure was planned to be used.

3.2.2.3 Subject Disposition, Demographic and Baseline Characteristics

Table 6. Study GSK-207660 subject disposition

	GSK1358820 240 U (N=63) n (%)	GSK1358820 400 U (N=61) n (%)	Total (N=124) n (%)
Subject Status			
Completed	57 (90)	56 (92)	113 (91)
Withdrawn	6 (10)	5 (8)	11 (9)
Primary Reason[1] for Study Withdrawal			
Adverse event	0	3 (5)	3 (2)
Protocol deviation	0	0	0
Subject reached protocol-defined stopping criteria	1 (2)	0	1 (<1)
Study closed/terminated	0	0	0
Lost to follow-up	0	0	0
Investigator discretion	0	0	0
Withdrew consent	5 (8)	2 (3)	7 (6)
Investigator site closed	0	0	0

Data Source: 207660 (Final) Table 1.15
1. Subjects could have only one primary reason.

Source: Table 13 in the clinical study report of Study GSK-207660

Table 6 presents the subject disposition of Study GSK-207660. A total of 131 subjects in Japan were screened, among which 124 randomized. Of the 124 subjects randomized, 61 (49%) were randomized to the Botox 500 U group, and 63 (51%) to the Botox 240 U group. Most (91%) subjects completed the study.

Table 7. Study GSK-207660 subject demographics, randomized population

	GSK1358820 240 U (N=63)	GSK1358820 400 U (N=61)	Total (N=124)
Sex, n (%)			
n	63	61	124
Female	10 (16)	15 (25)	25 (20)
Male	53 (84)	46 (75)	99 (80)
Age (YEARS)			
n	63	61	124
Mean (SD)	57.3 (10.98)	57.1 (9.90)	57.2 (10.42)
Median (Min, Max)	58.0 (21, 79)	56.0 (29, 73)	57.0 (21, 79)
Age Group (YEARS), n (%)			
n	63	61	124
≤18	0	0	0
19 - 64	46 (73)	45 (74)	91 (73)
≥65	17 (27)	16 (26)	33 (27)
Ethnicity, n (%)			
n	63	61	124
Hispanic or Latino	0	0	0
Not Hispanic or Latino	63 (100)	61 (100)	124 (100)
Race, n (%)			
n	63	61	124
Asian - Japanese Heritage	63 (100)	60 (98)	123 (>99)
Mixed race	0	1 (2)	1 (<1)

Source: selected from Table 17 in the clinical study report of Study GSK-207660

Table 7 summarizes the demographics of subjects in the randomized population. The two treatment groups appear similar in terms of sex, race, and age. The average age of all randomized subjects was 57.2 years (standard deviation (SD)=10.42). Almost all (99%) randomized population were Asian. There were more males (80%) than females (20%).

3.2.2.4 Results and Conclusions

Table 8. Study GSK-207660 analysis of responder proportion, ITT population

Treatment	N	Responder/n (%)	Difference from 240 U (%)	95% CI (%)
GSK1358820 240 U	63	32/63 (50.8%)	18.1	(1.1, 35.0)
GSK1358820 400 U	61	42/61 (68.9%)		

Source: Table 20 in the clinical study report of Study GSK-207660

Table 8 presents the analysis results of the proportion of responders in MAS score in elbow flexors at Week 6. The estimated difference between the groupwise proportions was 18.1%. Its 95% CI was (1.1%, 35.0%), indicating that the Botox 400 U group responded better than the Botox 240 U group.

Table 9. Study GSK-207660 analysis of the change from baseline in MAS score in elbow flexors, ITT population

Joint Visit	GSK1358820 240 U			GSK1358820 400 U			Difference from 240 U[1]	95% CI for Treatment Difference
	N (n)	Adjusted Mean	S.E. of Adjusted Mean	N (n)	Adjusted Mean	S.E. of Adjusted Mean		
Spasticity Gr-Elbow Flexion								
PERIOD 1 - V2 (Week 2)	63 (63)	-0.59	0.089	61 (60)	-1.07	0.102	-0.48	(-0.75, -0.22)
PERIOD 1 - V3 (Week 4)	63 (63)	-0.7	0.097	61 (59)	-1.12	0.110	-0.42	(-0.71, -0.13)
PERIOD 1 - V4 (Week 6)	63 (63)	-0.71	0.107	61 (59)	-1.09	0.128	-0.37	(-0.71, -0.04)
PERIOD 1 - V5 (Week 12)	63 (60)	-0.35	0.072	61 (57)	-0.61	0.101	-0.27	(-0.51, -0.02)

Source: selected from Table 24 in the clinical study report of Study GSK-207660

Table 9 presents the analysis results of the change from baseline in MAS scores in elbow flexors. The estimated differences between the Botox 400 U group and Botox 240 U group at Weeks 2, 4, 6, and 12, respectively. The directions of the estimated Botox-placebo differences favored the Botox 400 U group. The nominal p-values for testing the treatment difference at Weeks 2, 4, 6, and 12 were 0.0005, 0.0048, 0.027, and 0.0329, respectively.

3.3 Evaluation of Safety

Please refer to Dr. Susanne Goldstein's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 10. Study 191622-127 and Study GSK-207660 subgroup analyses by gender, ITT population

	Study 191622-127			Study GSK-207660	
MAS Score in the Elbow Flexors	**Botox 500 U**	**Botox 300 U**	**Placebo**	**Botox 400 U**	**Botox 240 U**
N at Week 6	16	18	17	59	63
Female					
n	3	8	10	13	10
Mean at baseline (SD)	4.0 (0.00)	4.0 (0.00)	4.1 (0.32)	4.1 (0.28)	4.1 (0.32)
Mean change from baseline at Week 6 (SD)	-2.7 (1.53)	-1.5 (1.31)	-0.7 (0.82)	-1.8 (0.99)	-1.0 (1.05)
Responder rate at Week 6	100% (3/3)	75% (6/8)	50% (5/10)	92% (12/13)	60% (6/10)
Male					
n	13	10	7	46	53
Mean at baseline (SD)	4.2 (0.38)	4.1 (0.32)	4.3 (0.49)	4.1 (0.28)	4.1 (0.30)
Mean change from baseline at Week 6 (SD)	-1.4 (1.39)	-1.4 (1.27)	-0.9 (1.21)	-0.9 (0.88)	-0.7 (0.85)
Responder rate at Week 6	69% (9/13)	70% (7/10)	43% (3/7)	65% (30/46)	49% (26/53)

Source: selected from the January 15, 2021 response to information request and March 30, 2021 response to information request

Table 11. Study 191622-127 and Study GSK-207660 subgroup analyses by age group, ITT population

	Study 191622-127			Study GSK-207660	
MAS Score in the Elbow Flexors	**Botox 500 U**	**Botox 300 U**	**Placebo**	**Botox 400 U**	**Botox 240 U**
N at Week 6	16	18	17	59	63
<65 years					
N	12	14	15	44	46
Mean at baseline (SD)	4.2 (0.39)	4.1 (0.27)	4.2 (0.41)	4.1 (0.32)	4.1 (0.25)
Mean change from baseline at Week 6 (SD)	-1.4 (1.44)	-1.4 (1.22)	-0.6 (0.83)	-1.1 (1.01)	-0.7 (0.91)
Responder rate at Week 6	67% (8/12)	71% (10/14)	40% (6/15)	70% (31/44)	52% (24/46)
≥65 years					
n	4	4	2	15	17
Mean at baseline (SD)	4.0 (0.00)	4.0 (0.00)	4.0 (0.00)	4.0 (0.00)	4.2 (0.39)
Mean change from baseline at Week 6 (SD)	-2.3 (1.50)	-1.8 (1.50)	-2.0 (1.41)	-1.1 (0.96)	-0.6 (0.86)
Responder rate at Week 6	75% (3/4)	100% (4/4)	100% (2/2)	73% (11/15)	47% (8/17)

Source: selected from the January 15, 2021 response to information request and March 30, 2021 response to information request

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Table 12. Study 191622-127 subgroup analyses by race, ITT population

MAS Score in the Elbow Flexors	Botox 500 U	Botox 300 U	Placebo
N at Week 6	16	18	17
Black			
n	3	2	6
Mean at baseline (SD)	4.33 (0.58)	4.33 (0.52)	4.00 (0.00)
Mean change from baseline at Week 6 (SD)	-1.33 (1.53)	-0.50 (0.71)	-0.67 (0.82)
Responder rate at Week 6	67% (2/3)	50% (1/2)	50% (3/6)
White			
n	10	13	9
Mean at baseline (SD)	4.10 (0.32)	4.08 (0.28)	4.11 (0.33)
Mean change from baseline at Week 6 (SD)	-2.20 (1.32)	-1.54 (1.27)	-1.00 (1.12)
Responder rate at Week 6	100% (10/10)	77% (10/13)	56% (5/9)
Other			
n	3	3	2
Mean at baseline (SD)	4.00 (0.00)	4.00 (0.00)	4.00 (0.00)
Mean change from baseline at Week 6 (SD)	0.00 (0.00)	-1.67 (1.53)	0.00 (0.00)
Responder rate at Week 6	0% (0/3)	67% (2/3)	0% (0/2)

Source: selected from the January 15, 2021 response to information request and analysis by the statistical reviewer

Table 10, **Table 11**, and **Table 12** present the analyses of the MAS scores in elbow flexors by gender, age group, and race, respectively, for Study 191622-127 and Study GSK-207660. All subjects in Study 191622-127 except one subject were from the US; none of the subjects in Study GSK-207660 was from the US and all subjects except one subject are Asian. Therefore, there are no subgroup analyses by geographic group for either study or subgroup analysis by race for Study GSK-207660 in this review. There is no compelling evidence from the subgroup analyses that a specific gender or age group benefits differently from Botox. The sample sizes of subjects who were non-white were too small to draw conclusions.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no major statistical issues that affect the approvability of this sBLA from a statistical standpoint.

5.2 Collective Evidence

Table 1 and **Table 2** provide the summary of the main efficacy results of Study 191622-127 and Study GSK-207660. The collective evidence from the two studies supports the addition of efficacy information of Botox for adult upper limb spasticity in the drug label in general. However, Study 191622-127 was terminated early: 53 subjects completed the study instead of the 423 subjects initially planned. The small sample size or large variability of this study appeared to result in an overestimated treatment effect, compared to the treatment effect obtained from the larger study GSK-207660.

5.3 Conclusions and Recommendations

Study 191622-127 and Study GSK-207660 provided statistical evidence that Botox is effective for the treatment of upper limb spasticity in adult patients. (b) (4)

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/s/

XIANGMIN ZHANG
07/09/2021 10:31:19 AM

KUN JIN
07/09/2021 12:12:35 PM
I concur with the review.

HSIEN MING J HUNG
07/09/2021 12:15:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103000Orig1s5320

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 13, 2021

To: Laura Jawidzik, Clinical Reviewer
Division of Neurology Products 1 (DN1)

Taura Holmes, Regulatory Project Manager, DN1

Tracy Peters, Associate Director for Labeling, DN1

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for BOTOX® (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use

BLA: 103000 s5320

In response to the DN2 consult request dated July 1, 2021, OPDP has reviewed the proposed product labeling (PI) BOTOX® (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use (Botox). This supplement (s5320) pertains to the indication for adult spasticity.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 on July 2, 2021 and are provided below.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

50 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

DHARA SHAH
07/13/2021 03:26:02 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 9, 2021
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	BLA 103000/S-5320
Product Name and Strength:	Botox (onabotulinumtoxinA) for Injection, 50 Units/vial, 100 Units/vial, and 200 Units/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Allergan, Inc.
FDA Received Date:	February 22, 2021
OSE RCM #:	2021-625
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA (Acting) Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

Allergan, Inc. submitted a Prior Approval Efficacy Supplement (BLA 103000/S-5320) for Botox (onabotulinumtoxinA) for Injection to add dosing guidance for 8 additional upper limb muscles within the approved muscle groups for adult upper limb spasticity. Subsequently, the Division of Neurology 1 (DN 1) requested that we review the proposed revisions to the Botox prescribing information (PI), and medication guide (MG) labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On December 9, 1991, Botox was approved under BLA 103000. Another prior approval supplement for this application was approved on February 9, 2021 (BLA 103000/S-5318). Thus, Allergan submitted revised Prescribing Information (PI) labeling for this supplement (S-5320), on February 22, 2021, incorporating the recently approved changes from BLA 103000/S-5318 and the edits in the proposed PI and Medication Guide (MG) on September 28, 2020.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 CONCLUSION

Our evaluation of the proposed Botox prescribing information (PI) and medication guide (MG) labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Botox that Allergan, Inc. submitted on February 22, 2021.

Table 2. Relevant Product Information for Botox	
Initial Approval Date	December 9, 1991
Active Ingredient	OnabotulinumtoxinA
Indication	• 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
Route of Administration	intramuscular, intradetrusor, or intradermal injection
Dosage Form	for Injection
Strength	50 Units, 100 Units, or 200 Units per vial
Dose and Frequency	• Follow indication-specific dosage and administration recommendations. In a 3 month interval, do not exceed a total dose of: o Adults: 400 Units o Pediatrics: the lesser of 10 Units/kg or 340 Units • See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection • Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor

	• Adult Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor • Pediatric Detrusor Overactivity associated with a Neurologic Condition: 0.5 mL injections across 20 sites into the detrusor o Greater than or equal to 34 kg: Recommended total dose is 200 Units o Less than 34 kg: Recommended total dose is 6 Units/kg • Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles • Adult Upper Limb Spasticity: Recommended total dose up to 400 Units divided among affected muscles • Adult Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles • Pediatric Upper Limb Spasticity: Recommended total dose 3 Units/kg to 6 Units/kg (maximum 200 Units) divided among affected muscles • Pediatric Lower Limb Spasticity: Recommended total dose 4 Units/kg to 8 Units/kg (maximum 300 Units) divided among affected muscles • Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients • Axillary Hyperhidrosis: 50 Units per axilla • Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye • Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX
How Supplied	powder supplied in a single-dose vial in the following sizes: • 50 Units • 100 Units • 200 Units
Storage	Unopened vials of BOTOX should be stored in a refrigerator between 2° to 8°C (36° to 46°F) for up to 36 months. Do not use after the expiration date on the vial. Reconstituted BOTOX may be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use
Container Closure	Botox is supplied in a single-dose vial. Each carton contains one vial.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 29, 2018,[a] we searched for previous DMEPA reviews using the term, Botox. Our search identified 10 previous reviews and 1 memo, and we confirmed our previous recommendations were considered or implemented. The results of our search and subsequent gap searches can be found in Appendix B of OSE RCM # 2017-2523, 2019-138, and 2020-820.[a,b,c]

On April 28, 2021, we conducted a gap search to identify any reviews finalized since our last search[c] using the term BLA 103000. Our search did not identify any additional reviews relevant to this review.

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[a] Morris, C. Label and Labeling Review for Botox (BLA 103000/S-05307). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 10. RCM No.: 2017-2523.

[b] Rider, B. Label and Labeling Review for Botox (BLA 103000/S-5309 & S-5310). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 11. RCM No.: 2019-138.

[c] Morris, C. Label and Labeling Review for Botox (BLA 103000/S-05318). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 13. RCM No.: 2020-820.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Botox labels and labeling submitted by Allergan, Inc. received on February 22, 2021.

- Prescribing Information (image not shown), available from: \\CDSESUB1\evsprod\bla103000\0442\m1\us\draft-labeling-track-changes-spasticity.doc
- Medication Guide

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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