Indications
BOTOX® is a prescription medicine that is injected into muscles to treat increased muscle stiffness in elbow, wrist, finger, thumb, ankle, and toe muscles in people 18 years and older with upper and lower limb spasticity.

It is not known whether BOTOX® is safe or effective to treat increased stiffness in upper limb muscles other than those in the elbow, wrist, fingers, and thumb, or in lower limb muscles other than those in the ankle and toes. BOTOX® has not been shown to help people perform task-specific functions with upper limbs or increase movement in joints that are permanently fixed in position by stiff muscles. BOTOX® is not meant to replace existing physical therapy or other rehabilitation that may have been prescribed.

IMPORTANT SAFETY INFORMATION
BOTOX® may cause serious side effects that can be life threatening. Get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX®:

- **Problems swallowing, speaking, or breathing**, due to weakening of associated muscles, can be severe and result in loss of life. You are at highest risk if these problems are pre-existing before injection. Swallowing problems may last several months.
- **Spread of toxin effects,** The effect of botulinum toxin may affect areas away from the injection site and cause serious symptoms including: loss of strength and all-over muscle weakness, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing.

Please see additional Important Safety Information about BOTOX® on following pages and accompanying full Product Information including Boxed Warning and Medication Guide.
IMPORTANT SAFETY INFORMATION (continued)

BOTOX® may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking BOTOX®. If this happens, do not drive a car, operate machinery, or do other dangerous activities. Do not take BOTOX® if you: are allergic to any of its ingredients (see Medication Guide for ingredients); had an allergic reaction to any other botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dyssport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA); have a skin infection at the planned injection site.
The dose of BOTOX® is not the same as, or comparable to, another botulinum toxin product. Serious and/or immediate allergic reactions have been reported, including itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Get medical help right away if you experience symptoms; further injection of BOTOX® should be discontinued. Please see additional Important Safety Information about BOTOX® on following pages.

What is spasticity?

Tightness and stiffness in your arms and legs caused by several conditions or neurologic events, including stroke, multiple sclerosis, traumatic brain injury, adult cerebral palsy, and spinal cord injury.

Here's what the different types of focal spasticity may look like

Upper limb spasticity

- "My fist got so tight."
- Bent elbow
- Bent wrist
- Clenched fist
- Thumb digging into palm

Lower limb spasticity

- "My ankle tightened and my toes curled up."
- Dropped foot
- Curled toes
- Bent wrist
- Turned in foot

Spasticity can affect just one body part—or you can have it in both your arms and your legs, and it can have a significant effect on your everyday life.
IMPORTANT SAFETY INFORMATION (continued)

Tell your doctor about all your muscle or nerve conditions such as ALS or Lou Gehrig’s disease, myasthenia gravis, or Lambert-Eaton syndrome, as you may be at increased risk of serious side effects including difficulty swallowing and difficulty breathing from typical doses of BOTOX®.

Tell your doctor if you have any breathing-related problems. Your doctor may monitor you for breathing problems during treatment with BOTOX®. The risk of developing lung disease in patients with reduced lung function is increased in patients receiving BOTOX®.

Bronchitis and upper respiratory tract infections (common colds) have been reported. Bronchitis was reported more frequently in people receiving BOTOX® for upper limb spasticity. Upper respiratory infections were also reported more frequently in people with prior breathing-related problems with spasticity.

Please see additional Important Safety Information about BOTOX® on following pages.

BOTOX® is injected to treat increased stiffness in elbow, wrist, finger, thumb, ankle, and toe muscles in adults with upper and lower limb spasticity. It is not known if BOTOX® is safe or effective to treat increased stiffness in upper and lower limb muscles other than in the elbow, wrist, fingers, thumb, ankle, and toes. BOTOX® has not been shown to help people perform task-specific functions with upper limbs or increase movement in joints permanently fixed in position by stiff muscles. BOTOX® is not meant to replace existing physical therapy or other rehabilitation that may have been prescribed.

Ask your doctor today if BOTOX® treatments could help with your Focal Spasticity
A real impact on real people

“I am filled with pride as I take on my challenges with symptoms, no matter how small they may seem. And that’s what I fight for: every small victory.”

“My fist was so tight and it was uncomfortable, so my doctor prescribed BOTOX®.

“My ankle got stiff and tight. That’s when my doctor suggested we try BOTOX®.

IMPORTANT SAFETY INFORMATION (continued)
Tell your doctor about all your medical conditions, including if you: have or have had bleeding problems; have plans to have surgery; had surgery on your face; weakness of forehead muscles; trouble raising your eyebrows; drooping eyelids; any other abnormal facial change; are pregnant or plan to become pregnant (it is not known if BOTOX® can harm your unborn baby); are breastfeeding or plan to (it is not known if BOTOX® passes into breast milk).

Please see additional Important Safety Information about BOTOX® on following pages.

LEARN THESE 3 WORDS TODAY

SPASTICITY
When muscles over tighten due to miscommunication between the brain and muscles. It’s caused by several conditions or neurologic events that can damage the brain or the spinal cord.

FOCAL
Your doctor may use this word. It means a problem or symptom that is focused on one specific area of your body. There are multiple types of spasticity and focal is one of them.

RE-TREATMENT
When multiple treatments of a medication are needed to determine which muscles to treat and the right dose to use.
What is it like to get BOTOX®?

MY FIRST YEAR OF TREATMENTS — DAN

I had a stroke about 2 years ago. It affected my right side, causing my wrist and fingers to clench up. Every day became a struggle with my symptoms, so I decided to talk with my doctor.

She suggested we try BOTOX® treatments. She explained how each patient was different and that it may take a few sessions to find the best approach and dose for me. At first I was hesitant about getting injections, but decided to give it a try.

Now, I go back about every 3 months for treatment. My doctor determines how much BOTOX® I need and what muscles need to be injected during those visits, based on how I am doing.

I still don’t like needles, but it’s done right in my doctor’s office, and it doesn’t take too long. I’ve been going back for over a year now and plan to keep going back as long as my doctor recommends. Keeping up with my treatment is important, so I always schedule my next appointment before leaving the doctor’s office.

CAREGIVERS’ CORNER

Where caregivers share their questions

Dear Doctor:
I am the primary caregiver for my 73-year-old mother who has Focal Spasticity in her right wrist and right ankle. What are some of the best ways I can help her? — Caring in Cleveland

Dear Caring in Cleveland:
One of the best ways you can help your mother is to watch her symptoms. You could rate her symptoms every week by asking yourself: Are her symptoms the same as last week, better, or worse? Let her doctor know what you observe.

Another good way to help your mother is to organize all her doctor’s appointments on a family calendar, and keep it in a place where you both can see it—such as the kitchen. Also, make sure she schedules follow-up appointments before she leaves the doctor’s office. That way you can both keep track and make sure she doesn’t miss any important appointments.

IMPORTANT SAFETY INFORMATION (continued)

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal products. Using BOTOX® with certain medicines may cause serious side effects. Do not start any new medicines until you have told your doctor that you received BOTOX® in the past.

Please see additional Important Safety Information about BOTOX® on following pages.
Did you know most insurance plans cover the majority of BOTOX® costs?*

In fact, patients with remaining out-of-pocket costs pay an average of $219 for BOTOX® for spasticity.
Did you know that BOTOX® can treat spasticity?
Your doctor does
Find out if it’s time to add BOTOX® to your treatment plan

*BOTOX® treatments may be repeated no sooner than every 12 weeks, once the previous treatment wears off.

IMPORTANT SAFETY INFORMATION (continued)
Other side effects of BOTOX® include: dry mouth, discomfort or pain at injection site, tiredness, headache, neck pain, and eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of eyelids, and dry eyes.

For more information refer to the Medication Guide or talk with your doctor.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Product Information including Boxed Warning and Medication Guide.
BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use

Initial U.S. Approval: 1989

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 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)
- Prophylaxis of headaches in adult patients with chronic migraine (>15 days per month with headache lasting ≥4 hours a day or longer) (1.2)
- Treatment of spasticity in adult patients (1.3)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)
- Treatment of strabismus in patients ≥12 years of age (1.6)

Important Limitations: Safety and effectiveness of BOTOX have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)
- Treatment of upper or lower limb spasticity in pediatric patients (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.5)

DOSEAGE AND ADMINISTRATION

- Dosage and Administration, Instructions for Safe Use (2.1) 05/2018

INDICATIONS AND USAGE

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 and strabismus (8.4)

Ayilary Hyperhidrosis: 50 Units per axilla (2.7)
Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.8)
Strabismus: The dose is based on prism dioptr correction or previous response to treatment with BOTOX (2.9)

Dosage and Administration

1 INDIcATIONS AND USAGE

1.1 Bladder Dysfunction
1.2 Chronic Migraine
1.3 Spasticity
1.4 Cervical Dystonia
1.5 Primary Axillary Hyperhidrosis
1.6 Blepharospasm and Strabismus

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use
2.2 Preparation and Dilution Technique
2.3 Bladder Dysfunction
2.4 Chronic Migraine
2.5 Spasticity
2.6 Cervical Dystonia
2.7 Primary Axillary Hyperhidrosis
2.8 Blepharospasm
2.9 Strabismus

Recent Major Changes

Dosage and Administration, Instructions for Safe Use (2.1) 05/2018

1.1 Bladder Dysfunction
1.2 Chronic Migraine
1.3 Spasticity
1.4 Cervical Dystonia
1.5 Primary Axillary Hyperhidrosis
1.6 Blepharospasm and Strabismus

Dosage and Administration

Initial U.S. Approval: 1989

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- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)
- Treatment of upper or lower limb spasticity in pediatric patients (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.5)

Dosage and Administration

Follow indication-specific dosage and administration recommendations; Do not exceed a total dose of 400 Units administered in a 3 month interval (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)

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)

Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.4)

Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.5)

Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)

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 naive patients (2.6)

Dosage and Administration

Dosage and Administration

Dosage and Administration, Instructions for Safe Use (2.1) 05/2018

Recent Major Changes

Dosage and Administration, Instructions for Safe Use (2.1) 05/2018

1.1 Bladder Dysfunction
1.2 Chronic Migraine
1.3 Spasticity
1.4 Cervical Dystonia
1.5 Primary Axillary Hyperhidrosis
1.6 Blepharospasm and Strabismus

Dosage and Administration

Initial U.S. Approval: 1989

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- 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)
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- Treatment of spasticity in adult patients (1.3)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
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Dosage and Administration

Follow indication-specific dosage and administration recommendations; Do not exceed a total dose of 400 Units administered in a 3 month interval (2.1)

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Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.5)

Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)

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 naive patients (2.6)
BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors, shoulder adductors, finger flexors, and hip flexors.

### Upper Limb Spasticity

BOTOX is indicated for the treatment of upper limb spasticity in adult patients to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors, shoulder adductors, finger flexors, and hip flexors.

### Lower Limb Spasticity

BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).

### Important Limitations

Safety and effectiveness of BOTOX have not been established for the treatment of other upper or lower limb muscle groups. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

## 1 INDICATIONS AND USAGE

### 1.1 Bladder Dysfunction

**Overactive Bladder**

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder 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 overactive bladder or detrusor overactivity associated with a neurologic condition in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

### 1.2 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 per day over ≥1 month).

### 1.3 Spasticity

#### Upper Limb Spasticity

BOTOX is indicated for the treatment of upper limb spasticity in adult patients to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), finger flexors (flexor digitorum profundus and flexor digitorum sublimis), and thumb flexors (adductor pollicis and flexor pollicis longus).

#### Lower Limb Spasticity

BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).
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 (100 Units and 200 Units)**

<table>
<thead>
<tr>
<th>Diluent* Added to 100 Unit Vial</th>
<th>Resulting Dose Units per 0.1 mL</th>
<th>Diluent* Added to 200 Unit Vial</th>
<th>Resulting Dose Units per 0.1 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mL</td>
<td>10 Units</td>
<td>1 mL</td>
<td>20 Units</td>
</tr>
<tr>
<td>2 mL</td>
<td>5 Units</td>
<td>2 mL</td>
<td>10 Units</td>
</tr>
<tr>
<td>4 mL</td>
<td>2.5 Units</td>
<td>4 mL</td>
<td>5 Units</td>
</tr>
<tr>
<td>8 mL</td>
<td>1.25 Units</td>
<td>8 mL</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>10 mL</td>
<td>1 Unit</td>
<td>10 mL</td>
<td>2 Units</td>
</tr>
</tbody>
</table>

* 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 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

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 exceed the recommended dose of 200 Unit Vial of BOTOX.

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 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 2 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.
Table 2: BOTOX Dosing by Muscle for Chronic Migraine

| Head/Neck Area | Recommended Dose (Number of Sites)
|----------------|-----------------------------------
| Frontalis a | 20 Units divided in 4 sites |
| Corrugator a | 10 Units divided in 2 sites |
| Procerus a | 5 Units in 1 site |
| Occipitalis a | 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

2.5 Spasticity

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 or nerve stimulation 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.

Upper Limb Spasticity

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 3 and Figure 2) at a given treatment session.

Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity

| Muscle | Recommended Dose Total Dosage (Number of Sites)
|--------|-----------------------------------
| Biceps Brachii | 100 Units-200 Units divided in 4 sites |
| Flexor Carpi Radialis | 12.5 Units-50 Units in 1 site |
| Flexor Carpi Ulnaris | 12.5 Units-50 Units in 1 site |
| Flexor Digitorum Profundus | 30 Units-50 Units in 1 site |
| Flexor Digitorum Sublimis | 30 Units-50 Units in 1 site |
| Adductor Pollicis | 20 Units in 1 site |
| Flexor Pollicis Longus | 20 Units in 1 site |

Lower Limb Spasticity

The recommended dose for treating 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 4 and Figure 3).

Table 4: BOTOX Dosing by Muscle for 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 |

2.6 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 (14.5)).

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 (5.2, 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.

2.7 Primary Auxiliary 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 4.

Figure 4: Injection Pattern for Primary Auxiliary 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.

2.8 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. Ectopy 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 100 Units/8 mL; for 2.5 Units it is 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.

2.9 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 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

3. DOSAGE FORMS AND STRENGTHS

For Injection: 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

4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation (see Warnings and Precautions (5.4)).

4.2 Infection at the Injection Site(s)

BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

4.3 Urinary Tract Infection or Urinary Retention

Intradetrusor injection of BOTOX is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection. Intradetrusor injection of BOTOX is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200 mL, who are not routinely performing clean intermittent self-catheterization (CIC).
In 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 6).

Table 6: 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

<table>
<thead>
<tr>
<th>Week 2</th>
<th>0/15 (0%)</th>
<th>0/15 (0%)</th>
<th>1/11 (9%)</th>
<th>0/11 (0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>2/13 (15%)</td>
<td>1/3 (8%)</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
<td>0/7 (0%)</td>
<td>0/7 (0%)</td>
</tr>
</tbody>
</table>

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 patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In 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 event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

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 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 Patients 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, persistent 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 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 7. The duration of post-injection catheterization for those who developed urinary retention is also shown.
Table 7: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB

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

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 8.

Table 8: Proportion of Patients Experiencing Urinary Retention Following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB According to History of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX 100 Units (N=81)</td>
</tr>
<tr>
<td></td>
<td>BOTOX 100 Units (N=526)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td>12.3% (n=10)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.6% (n=3)</td>
</tr>
</tbody>
</table>

Detrusor Overactivity associated with a Neurologic Condition

In two double-blind, placebo-controlled trials in 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 9. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 9: Proportion of 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

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BOTOX 200 Units (N=109)</th>
<th>Placebo (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Patients Catheterizing for Urinary Retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At any time during complete treatment cycle</td>
<td>30.6% (n=33)</td>
<td>6.7% (n=7)</td>
</tr>
<tr>
<td>Duration of Catheterization for Urinary Retention (Days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>289</td>
<td>358</td>
</tr>
<tr>
<td>Min, Max</td>
<td>1, 530</td>
<td>2, 379</td>
</tr>
</tbody>
</table>

Among 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 10).

Table 10: Proportion of 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

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>MS</th>
<th>SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX 200 Units (N=86)</td>
<td>Placebo (N=88)</td>
</tr>
<tr>
<td>At any time during complete treatment cycle</td>
<td>31% (n=27)</td>
<td>5% (n=4)</td>
</tr>
</tbody>
</table>

A placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) was conducted in non-catheterizing 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 (5.2)]
- Serious Adverse Reactions with Unapproved Use [see Warnings and Precautions (5.9)]
- Hypersensitivity Reactions [see Contraindications (4.1) 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 [see Warnings and Precautions (5.6)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- 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, 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 (5.2)].

Overactive Bladder

Table 11 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 11: 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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 100 Units (N=552)</th>
<th>Placebo (N=542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>99 (18%)</td>
<td>30 (6%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>50 (9%)</td>
<td>36 (7%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>31 (6%)</td>
<td>2 (0%)</td>
</tr>
<tr>
<td>Bacteriuria</td>
<td>24 (4%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Residual urine volume*</td>
<td>17 (3%)</td>
<td>1 (0%)</td>
</tr>
</tbody>
</table>

* 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 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 14 presents the most frequently reported adverse reactions within 12 weeks of injection. The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 17.

**Table 12: 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**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BOTOX 100 Units (N=81)</th>
<th>Placebo (N=69)</th>
<th>BOTOX 100 Units (N=526)</th>
<th>Placebo (N=510)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection (UTI)</td>
<td>25 (31%)</td>
<td>8 (12%)</td>
<td>135 (26%)</td>
<td>51 (10%)</td>
</tr>
</tbody>
</table>

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.

**Detrusor Overactivity associated with a Neurologic Condition**

Table 13 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 13: Adverse Reactions Reported by ≤2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradermal Injection in Double-blind, Placebo-controlled Clinical Trials**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 200 Units (N=262)</th>
<th>Placebo (N=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>64 (24%)</td>
<td>47 (17%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>45 (17%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Hematura</td>
<td>10 (4%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

**Table 14: 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 Intradermal Injection**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 100 Units (N=115)</th>
<th>Placebo (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>17 (26%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Bacteruria</td>
<td>6 (9%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>10 (15%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>3 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Residual urine volume*</td>
<td>11 (17%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

* 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%), bacteruria (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).

**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 15.

**Table 15: 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**

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX 155 Units-195 Units (N=687)</th>
<th>Placebo (N=692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32 (5%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>25 (4%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (3%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (9%)</td>
<td>19 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (3%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>23 (3%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (2%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

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.

**Upper Limb Spasticity**

The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 16.

**Table 16: 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**

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX 251 Units-360 Units (N=115)</th>
<th>BOTOX 150 Units-250 Units (N=188)</th>
<th>BOTOX &lt;150 Units (N=54)</th>
<th>Placebo (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (3%)</td>
<td>3 (2%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (3%)</td>
<td>4 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4 (3%)</td>
<td>4 (2%)</td>
<td>0</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>7 (6%)</td>
<td>10 (5%)</td>
<td>5 (9%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>0</td>
<td>7 (4%)</td>
<td>1 (2%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

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.

**Lower Limb Spasticity**

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 17.

**Table 17: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Chronic Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trials**
Table 17: 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 6)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX (N=231)</th>
<th>Placebo (N=233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (3%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Infecions and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
</tbody>
</table>

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%).

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 ovariative 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 analyzed specimens in the 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.

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 Post-Marketing 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; hyperhidrosis; hypoacusia; 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 fetal ossification) and was associated with maternal toxicity [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage is about 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 twice 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

Bladder Dysfunction

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

Prophylaxis of Headaches in Chronic Migraine

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

8.5 Geriatric Use

Oral Botox is less effective in elderly patients compared to younger patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Table 18: 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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>&lt;65 Years</th>
<th>65 to 74 Years</th>
<th>≥75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units</td>
<td>73 (21%)</td>
<td>23 (7%)</td>
<td>51 (30%)</td>
</tr>
<tr>
<td>Placebo 100 Units</td>
<td>21 (6%)</td>
<td>2 (0.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Placebo 155 Units</td>
<td>21 (6%)</td>
<td>2 (0.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>BOTOX 100 Units</td>
<td>36 (38%)</td>
<td>16 (19%)</td>
<td></td>
</tr>
<tr>
<td>Placebo 155 Units</td>
<td>8 (9%)</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

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 (5.2, 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 (LD₅₀) 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/mg of neurotoxin protein complex.

Each vial of BOTOX (onabotulinumtoxinA) for injection contains either 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 toxicity 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, 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 weekly BOTOX injections resulting in a total of 130 Units/kg (~44X the highest human bladder dose) to the base of the bladder as a 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).

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 19 and Table 20, and Figure 5 and Figure 6.

Table 19: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units (N=278)</th>
<th>Placebo (N=272)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 2</td>
<td>-2.6</td>
<td>-1.0</td>
<td></td>
<td>-1.6</td>
</tr>
<tr>
<td>Mean Change at Week 6</td>
<td>-2.8</td>
<td>-1.0</td>
<td></td>
<td>-1.8</td>
</tr>
<tr>
<td>Mean Change at Week 12**</td>
<td>-2.5</td>
<td>-0.9</td>
<td></td>
<td>-1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-2.1, -1.2)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 20: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units (N=275)</th>
<th>Placebo (N=269)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 2</td>
<td>-2.7</td>
<td>-1.1</td>
<td></td>
<td>-1.6</td>
</tr>
<tr>
<td>Mean Change at Week 6</td>
<td>-3.1</td>
<td>-1.3</td>
<td></td>
<td>-1.8</td>
</tr>
<tr>
<td>Mean Change at Week 12**</td>
<td>-3.0</td>
<td>-1.1</td>
<td></td>
<td>-1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-2.5, -1.4)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* 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.

References
1. 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
† Primary variable
† Secondary variable

Table 18: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units (N=278)</th>
<th>Placebo (N=272)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline</td>
<td>12.0</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12**</td>
<td>-1.9</td>
<td>-0.9</td>
<td>(-1.5, -0.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 17: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units (N=275)</th>
<th>Placebo (N=269)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline</td>
<td>156</td>
<td>161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12**</td>
<td>38</td>
<td>8</td>
<td>30 (17, 43)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* 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.

† Primary variable
‡ Secondary variable
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 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 urinary 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 21 and Table 22, and Figure 7 and Figure 8. No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

**Table 21: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-1**

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
<th>Treatment Difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>134</td>
<td>146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.3</td>
<td>28.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-15.3</td>
<td>-10.0</td>
<td>-5.3</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-19.9</td>
<td>-10.6</td>
<td>-9.2 (-13.1, -5.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-19.8</td>
<td>-8.8</td>
<td>-11.0</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>123</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>253.8</td>
<td>259.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>135.9</td>
<td>12.1</td>
<td>123.9 (89.1, 158.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>41</td>
<td>103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>63.1</td>
<td>57.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-28.1</td>
<td>-3.7</td>
<td>-24.4</td>
<td></td>
</tr>
</tbody>
</table>

* 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
* Primary endpoint
* Secondary endpoint

**Table 22: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-2**

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
<th>Treatment Difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>91</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.7</td>
<td>36.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-18.0</td>
<td>-7.9</td>
<td>-10.1</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-19.6</td>
<td>-10.8</td>
<td>-8.8 (-14.5, -3.0)</td>
<td>p=0.003</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-19.6</td>
<td>-10.7</td>
<td>-8.9</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>88</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>239.6</td>
<td>253.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>150.8</td>
<td>2.8</td>
<td>148.0 (101.8, 194.2)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>65.6</td>
<td>43.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-28.7</td>
<td>2.1</td>
<td>-30.7</td>
<td></td>
</tr>
</tbody>
</table>

* 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
* Primary endpoint
* Secondary endpoint
The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 285-337 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 23.

### Table 23: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-3

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units</th>
<th>Placebo</th>
<th>Treatment Difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>66</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>4.2</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-2.9</td>
<td>-1.2</td>
<td>-1.7</td>
<td>—</td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-3.4</td>
<td>-1.1</td>
<td>-2.3 (-3.0, -1.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-2.7</td>
<td>-1.0</td>
<td>-1.8</td>
<td>—</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>62</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>248.9</td>
<td>245.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>134.4</td>
<td>3.5</td>
<td>130.9 (94.8, 167.0)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>25</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>42.4</td>
<td>39.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-19.2</td>
<td>2.7</td>
<td>-21.9 (-37.5, -6.3)</td>
<td></td>
</tr>
</tbody>
</table>

* 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

* 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 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 >15 headache days lasting 4 hours or more, with >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 24).

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

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX (N=341)</td>
<td>Placebo (N=338)</td>
</tr>
<tr>
<td></td>
<td>BOTOX (N=347)</td>
<td>Placebo (N=358)</td>
</tr>
<tr>
<td><strong>Efficacy per 28 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in frequency of headache days</td>
<td>-7.8*</td>
<td>-6.4</td>
</tr>
<tr>
<td>Change from baseline in total cumulative hours of headache on headache days</td>
<td>-107*</td>
<td>-70</td>
</tr>
</tbody>
</table>

* Significantly different from placebo (p<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 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.

**Figure 9: Mean Change from Baseline in Number of Headache Days for Study 1**

![Chart showing mean change from baseline in number of headache days for Study 1]

**Figure 10: Mean Change from Baseline in Number of Headache Days for Study 2**

![Chart showing mean change from baseline in number of headache days for Study 2]

**14.4 Spasticity**

**Upper Limb Spasticity**

The efficacy of BOTOX for the treatment of upper limb spasticity was evaluated in three randomized, multi-center, double-blind, placebo-controlled studies (Studies 1, 2, and 3). Two additional randomized, multi-center, double-blind, placebo-controlled studies for upper limb spasticity in adults also included the evaluation of the efficacy of BOTOX for the treatment of thumb spasticity (Studies 4 and 5).

Study 1 included 126 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 weeks post-stroke. BOTOX and placebo were injected into the adductor pollicis and flexor pollicis longus muscles.

Study 2 compared 3 doses of BOTOX with placebo and included 91 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 3 for wrist flexor tone and at least 2 for elbow flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus and flexor digitorum sublimis muscles.

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 26.

**Table 26: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>BOTOX (N=64)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†*</td>
<td>-2.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††</td>
<td>-1.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale††</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>Median Physician Global Assessment of Response to Treatment††</td>
<td>2.0*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1 Primary endpoint at Week 6
2 Secondary endpoint at Week 6
* Significant difference from placebo (p≤0.05)
†† BOTOX injected into both the flexor carpi radialis and ulnaris muscles
b BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
B BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

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 28.

**Table 27: Study Medication Dose and Injection Sites in Study 2 and Study 3**

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Total Dose</th>
<th>Volume (mL)</th>
<th>Injection Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX low dose (90 Units)</td>
<td>0.4</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>BOTOX mid dose (180 Units)</td>
<td>0.6</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>BOTOX high dose (360 Units)</td>
<td>0.3</td>
<td>100</td>
<td>4</td>
</tr>
</tbody>
</table>

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 28.

**Table 25: Study Medication Dose and Injection Sites in Study 1**

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Volume (mL)</th>
<th>BOTOX (Units)</th>
<th>Number of Injection Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist Flexor Carpi Radialis</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Finger Flexor Digitorum Profundus</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis†</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Pollicis Longus‡</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

† Injected only if spasticity is present in this muscle
‡ Injected only if spasticity is present in this muscle
Study 4 included 170 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 30). Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, 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 30). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

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 31. The MAS uses a similar scoring system as the Ashworth Scale.

Table 30: Study Medication Dose and Injection Sites in Studies 4 and 5

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(mL)</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke 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 33) 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 31: Efficacy Endpoint for Knee Flexion on the Ashworth Scale at Week 6 in Study 5

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(mL)</td>
</tr>
<tr>
<td>Knee Flexor</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Study 6 included 468 post-stroke 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 33) 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 32: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(mL)</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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 31. The MAS uses a similar scoring system as the Ashworth Scale.

Table 33: Efficacy Endpoints for Knee Flexion on the Ashworth Scale at Week 6 in Study 5

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(mL)</td>
</tr>
<tr>
<td>Knee Flexor</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Study 6 included 468 post-stroke 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 33) 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 34: Efficacy Endpoints for Knee Flexion on the Ashworth Scale at Week 6 in Study 5

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(mL)</td>
</tr>
<tr>
<td>Knee Flexor</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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 31. The MAS uses a similar scoring system as the Ashworth Scale.

The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke 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 33) 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.

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<tr>
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<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(mL)</td>
</tr>
<tr>
<td>Knee Flexor</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
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<td>20</td>
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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 34).

Table 34: Co-Primary Efficacy Endpoints Results in Study 6 (Intent-to-treat Population)

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>BOTOX (Units)</th>
<th>Placebo (N=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory Ankle Muscles</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Gastrocnemius (medial head)</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Gastrocnemius (lateral head)</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Soleus</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Optional Muscles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor Hallucis Longus</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Flexor Digitum Longus</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Flexor Digitum Brevis</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Extensor Hallucis</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Rectus Femoris</td>
<td>100</td>
<td>3</td>
</tr>
</tbody>
</table>

* Significantly different from placebo (p<0.05)

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 11) and CGI (see Figure 12) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

Figure 11: Modified Ashworth Scale Ankle Score for Study 6 – Mean Change from Baseline by Visit

Figure 12: Clinical Global Impression by Physician for Study 6 – Mean Scores by Visit

14.5 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 35.

Table 35: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

<table>
<thead>
<tr>
<th>Baseline CDSS</th>
<th>BOTOX (N=88)</th>
<th>Placebo (N=82)</th>
<th>95% CI on Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in CDSS at Week 6</td>
<td>-0.3</td>
<td>-1.3</td>
<td>(-2.3, 0.3)*a</td>
</tr>
<tr>
<td>% Patients with Any Improvement on Physician Global Assessment</td>
<td>31%</td>
<td>51%</td>
<td>(5%, 34%)*a</td>
</tr>
<tr>
<td>Pain Intensity Baseline</td>
<td>1.8</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Change in Pain Intensity at Week 6</td>
<td>-0.4</td>
<td>-0.1</td>
<td>(-0.7, -0.2)*b</td>
</tr>
<tr>
<td>Pain Frequency Baseline</td>
<td>1.6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Change in Pain Frequency at Week 6</td>
<td>-0.3</td>
<td>-0.0</td>
<td>(-0.5, -0.0)*b</td>
</tr>
</tbody>
</table>

*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.

10 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 2 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 36. The total dose and muscles selected were tailored to meet individual patient needs.

**Table 36: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles**

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

* 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.

14.6 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 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”; 2 = “underarm sweating is tolerable and generally interferes with my daily activities”; 3 = “underarm sweating is noticeable and frequently interferes with my daily activities”; and 4 = “underarm sweating is intolerable and always interferes with my daily activities”.

The efficacy of the treatment was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were defined as 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 37).

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 37: Study 1 - Study Outcomes**

<table>
<thead>
<tr>
<th>Treatment Response</th>
<th>BOTOX 50 Units (N=104)</th>
<th>BOTOX 75 Units (N=110)</th>
<th>Placebo (N=108)</th>
<th>BOTOX placebo (95% CI)</th>
<th>BOTOX 75-placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDSS Score change ≥2 (%)</td>
<td>55% (57)</td>
<td>49% (54)</td>
<td>6% (6)</td>
<td>49.3% (38.8, 59.7)</td>
<td>43% (33.2, 53.8)</td>
</tr>
<tr>
<td>&gt;50% decrease in axillary sweat production % (n)</td>
<td>81% (84)</td>
<td>86% (94)</td>
<td>41% (44)</td>
<td>40% (28.1, 52.0)</td>
<td>45% (33.3, 56.1)</td>
</tr>
</tbody>
</table>

* 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.

14.7 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.

14.8 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
BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried powder supplied in a single-dose vial in the following sizes: 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.

**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 [see Dosage and Administration (2.2)].

**17 PATIENT COUNSELING INFORMATION**
Advise the patient to read the FDA-approved patient labeling (Medication Guide), Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms
Advise patients 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 Precautions (5.2, 5.6)].

**Ability to Operate Machinery or Vehicles**
Advise patients 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.
MEDICATION GUIDE

BOTOX®
BOTOX® Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for Injection

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 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?”

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 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 elbow, wrist, and finger muscles in adults with upper limb spasticity.
• to treat increased muscle stiffness in ankle and toe muscles in adults with lower limb 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 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 or effective in people younger than:

• 18 years of age for treatment of urinary incontinence
• 18 years of age for treatment of chronic migraine
• 18 years of age for treatment of spasticity
• 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

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 or 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 or effective for other types of muscle spasms or 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 list of ingredients in BOTOX and BOTOX Cosmetic.
• had an allergic reaction to any other botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
• 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) and/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 people being treated for urinary incontinence
• painful urination in people 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.

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 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 healthcare professionals.

What are the ingredients in BOTOX and BOTOX Cosmetic?
Active ingredient: onabotulinumtoxinA
Inactive ingredients: human albumin and sodium chloride

Revised: 05/2018

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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