INDICATION
BOTOX® (onabotulinumtoxinA) is a prescription medicine that is injected into muscles and used to treat abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

IMPORTANT SAFETY INFORMATION
BOTOX® may cause serious side effects that can be life threatening. Call your doctor or 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 the highest risk if these problems are pre-existing before injection. Swallowing problems may last for 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 (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing. If this happens, do not drive a car, operate machinery, or do other dangerous activities

There has not been a confirmed serious case of spread of toxin effect away from the injection site when BOTOX® has been used at the recommended dose to treat blepharospasm or strabismus.

Please see additional Important Safety Information about BOTOX® on the following pages and accompanying full Product Information including Boxed Warning and Medication Guide on page 13.
The basics of blepharospasm

Unable to open your eye. Blinking with no end. Spasms you just can’t control. If you experience these intrusive symptoms, you may have blepharospasm. This condition can be difficult to understand and a challenge to live with.

IMPORTANT SAFETY INFORMATION (Continued)

Do not take BOTOX® (onabotulinumtoxinA) if you: are allergic to any of the ingredients in BOTOX® (see Medication Guide for ingredients); had an allergic reaction to any other botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dysport® (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.

Please see additional Important Safety Information on the following pages and accompanying full Product Information including Boxed Warning and Medication Guide on page 13.
About blepharospasm

**Blepharospasm** is characterized by involuntary spasms of the muscles around the eye, resulting in uncontrolled blinking, narrowing, and even closing of the eyelid.¹

**The signs of blepharospasm**

In the early stages of blepharospasm, you may feel irritation and discomfort of the eyelids as well as increased blinking.¹

Possible early symptoms:
- Dry eyes¹ or watering eyes²
- Light sensitivity³
- Increased blinking¹
- Ocular pain²
- Soreness around the eyes²

It is unknown what exactly causes the muscle contractions characteristic of blepharospasm.¹

**How it’s diagnosed**

**Specialists** like neurologists and ophthalmologists diagnose blepharospasm based on specific signs and symptoms.²
INDICATION

BOTOX® is a prescription medicine that is injected into muscles and used to treat abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

IMPORTANT SAFETY INFORMATION (Continued)

Serious and/or immediate allergic reactions have been reported. These reactions 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 experience any such symptoms; further injection of BOTOX® (onabotulinumtoxinA) should be discontinued.

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

Please see additional Important Safety Information on the following pages and accompanying full Product Information including Boxed Warning and Medication Guide on page 13.
An effective treatment for 25 years

You may be interested to learn that BOTOX® (onabotulinumtoxinA) has been used for 25 years, and has been a treatment option for blepharospasm and its symptoms since 1989. BOTOX® is approved to help relieve the eyelid muscle spasms associated with blepharospasm. There are 3 clinical studies that were conducted to determine how effective BOTOX® is in treating blepharospasm.

- In one study approximately 90% of patients (25 out of 27) showed an improvement within 2 days
- In another study, doctors noted less force was needed to hold the patients’ eyelids open during examinations (as measured by a 2-point change on a clinical study scale)

An affordable option for many

In addition to being an effective treatment, BOTOX® can be an affordable option. To find out more information on getting help with your BOTOX® treatment costs simply turn to pages 8-9 of this brochure.

Did you know?

Allergan, the maker of BOTOX®, has a savings card that may help you save on your out-of-pocket costs.

Talk to your doctor today to see if BOTOX® may be an option for you.

See the “Let’s Talk Blepharospasm” guide on page 11.
How BOTOX® (onabotulinumtoxinA) works

To treat blepharospasm, BOTOX® therapy helps block signals from the nerves that tell the muscles that control the affected areas to contract. This helps reduce eye muscle spasms.4

See results as soon as 3 days

When you treat blepharospasm with BOTOX® therapy, you may begin seeing an improvement in your symptoms within the first 3 days, with maximum results about 1 to 2 weeks after your injection.4

Treatment once every 3 months

There is no daily treatment required with BOTOX®.4 Your specialist will administer BOTOX® treatments by injecting the medicine directly into your affected muscles.4 You can get treated again by your specialist after the effect of the previous injection has worn off, but no sooner than every 3 months.4

IMPORTANT SAFETY INFORMATION (Continued)

Cornea problems have been reported. Cornea (surface of the eye) problems have been reported in some people receiving BOTOX® for their blepharospasm, especially in people with certain nerve disorders. BOTOX® may cause the eyelids to blink less, which could lead to the surface of the eye being exposed to air more than is usual. Tell your doctor if you experience any problems with your eyes while receiving BOTOX®. Your doctor may treat your eyes with drops, ointments, contact lenses, or with an eye patch.

Please see additional Important Safety Information on the following pages and accompanying full Product Information including Boxed Warning and Medication Guide on page 13.
Possible side effects

The needles used for BOTOX® (onabotulinumtoxinA) injections are very fine, but you may experience some pain, swelling, and other reactions at the injection sites. In a clinical study of patients who received BOTOX® treatment for blepharospasm, the most frequently reported adverse reactions were droopy eyelid, cornea (surface of the eye) problems, and eye dryness.

Other events reported in prior clinical studies include: irritation, tearing, eyelid disorders, sensitivity to light, inflammation of the cornea, double vision, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

BOTOX® may cause serious side effects that can be life threatening. Call your doctor or 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 the highest risk if these problems are pre-existing before injection. Swallowing problems may last for 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 (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing. If this happens, do not drive a car, operate machinery, or do other dangerous activities.

This list does not cover all the possible serious side effects of BOTOX®. Please refer to the full Product Information, including Boxed Warning and Medication Guide on page 13, and talk with your doctor.

Talk to your doctor today to see if BOTOX® may be an option for you.

See the “Let’s Talk Blepharospasm” guide on page 11.
Ways to save on your treatment

Many insurance plans, including Medicare and Medicaid, cover BOTOX® (onabotulinumtoxinA) treatment for blepharospasm. It’s important to learn about your options so you can get effective and affordable care.

Allergan also offers two programs to help with treatment costs: the BOTOX® Savings Card and BOTOX PATIENT ASSISTANCE®. See the chart below for details:

<table>
<thead>
<tr>
<th></th>
<th>Commercially Insured Patients</th>
<th>Uninsured and Underinsured Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program Name</td>
<td>BOTOX® Savings Card</td>
<td>BOTOX PATIENT ASSISTANCE®</td>
</tr>
<tr>
<td>Coverage</td>
<td>Up to $100 per treatment for  out-of-pocket expenses*</td>
<td>The full cost of BOTOX®</td>
</tr>
</tbody>
</table>

Patients are subject to eligibility criteria. *Offer is valid for up to 4 treatments in a 12-month period.

Your BOTOX® Savings Card may only be used at hospitals, physician offices, and pharmacies, and will not be accepted at any other location that normally accepts Visa® Debit cards. “Metropolitan Commercial Bank” and “Metropolitan” are registered trademarks of Metropolitan Commercial Bank © 2014. The BOTOX® Savings Card cannot be used at merchants outside the United States (including Internet and mail/telephone merchants). The BOTOX® Savings Card is issued by Metropolitan Commercial Bank, member FDIC, pursuant to license by Visa USA, Inc. See the Cardholder Agreement for Terms and Conditions. By accepting, signing, or using this savings card, you agree to the Terms and Conditions of the Cardholder Agreement. This savings card will remain the property of the issuing institution and the privilege of its use may be withdrawn at any time.

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, such as 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 breastfeed (it is not known if BOTOX® passes into breast milk).

Please see additional Important Safety Information on the following pages and accompanying full Product Information including Boxed Warning and Medication Guide on page 13.
Support is here, with Patient Assistance Programs

Allergan, the maker of BOTOX®, is committed to helping you receive timely, appropriate treatment. We offer a variety of ways to assist you through our Patient Assistance Programs:

- The BOTOX PATIENT ASSISTANCE® Program provides BOTOX® treatment at no charge to financially eligible people (uninsured or underinsured) who can’t otherwise afford treatment.

- The BOTOX® Savings Card is available for eligible people with commercial insurance who need assistance with their out-of-pocket costs for BOTOX® treatment, beyond what their insurance will cover.

Eligibility requirements:

To receive help from the BOTOX® Savings Card patients must:

- Be 18 years or older, commercially insured and receiving BOTOX® for a therapeutic use
- Receive an Explanation of Benefits from their insurance company verifying BOTOX® treatment and/or a receipt from the Specialty Pharmacy Provider (SPP)*
- Not be enrolled in or eligible for Medicare, Medicaid, or any other federal or state government healthcare program

*An EOB or SPP receipt is not necessary during enrollment, but will be required when you submit a claim to receive funds on your BOTOX® Savings Card.

If you think you may be eligible:

Call 1-800-44-BOTOX, and then select Option 4 when you are prompted.
Or you can visit our Web site: BOTOXSavingsCard.com

TERMS AND CONDITIONS

By participating, you understand and agree to comply with the Program rules as set forth below.

Offer is valid only for BOTOX® and BOTOX® treatment-related costs not covered by your insurance plan. The BOTOX® Savings Card will be funded upon approval of your claim. Your claim must be submitted with your Explanation of Benefits (EOB) or your Specialty Pharmacy Provider (SPP) receipt. (If your BOTOX® prescription was filled by a Specialty Pharmacy Provider, you must send both your EOB and SPP receipt.)

All claims must be submitted within 90 days of the date of service listed on the EOB. BOTOX® Savings Card may not be combined with any other offer or discount. This BOTOX® Savings Card is not health insurance.

Offer not valid for patients participating in Medicare, Medicaid, or any similar federal or state healthcare program, including any state medical or pharmaceutical assistance programs. If patients are eligible for drug benefits under any such program, they cannot use this BOTOX® Savings Card.

Offer void where prohibited by law, taxed, or restricted. Offer good only in the United States. Allergan, Inc., reserves the right to rescind, revoke, and amend this offer without notice.
Use the “Let’s Talk Blepharospasm” guide to talk with your doctor

Find out if BOTOX® (onabotulinumtoxinA) can help with muscle contractions around your eyelids. Use the “Let’s Talk Blepharospasm” guide on the next page to start a conversation with your doctor or ask your doctor to recommend a specialist.

IMPORTANT SAFETY INFORMATION (Continued)

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal products. Using BOTOX® 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® in the past.

Especially tell your doctor if you: have received any other botulinum toxin product in the last 4 months; have received injections of botulinum toxin such as Myobloc®, Dysport®, or Xeomin® in the past (be sure your doctor knows exactly which product you received); have recently received an antibiotic by injection; take muscle relaxants; take an allergy or cold medicine; take a sleep medicine; take anti-platelets (aspirin-like products) or anti-coagulants (blood thinners).

Other side effects of BOTOX® (onabotulinumtoxinA) include: dry mouth, discomfort or pain at the injection site, tiredness, headache, neck pain, and eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your 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 on page 13.
Let's Talk Blepharospasm
Questions to help you start a conversation with your doctor

Review the questions below, and then discuss your answers with your doctor.

1. Do you have any of the following symptoms? (Check all that apply)
   - Eye twitching or ticks
   - Repetitive blinking
   - Involuntary closing of my eyelids
   - Eye irritation or discomfort
   - Dry or watering eyes
   - Eye pain
   - Symptoms get worse with light, noise, stress, polluted air, and/or wind

2. If you have difficulty with everyday tasks, which ones do you find difficult?
   - Driving a car
   - Watching television
   - Using a computer
   - Reading
   - Other

3. Would you be willing to talk to your doctor about BOTOX® (onabotulinumtoxinA)?
   - Yes
   - No

Talk to your doctor today to see if BOTOX® may be an option for you.

See the “Let’s Talk Blepharospasm” guide on this page.
WARNING: DISTANT SPREAD OF TOXIN EFFECT

The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. (5.2)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use

Initial U.S. Approval: 1989

Lawrence O. Lisker, M.D., Ph.D.

DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection USP prior to injection (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.4, 6)
- Infection at the proposed injection site (4.2)
- Intradetrusor injections: Urinary Tract Infection or Urinary Retention (4.3)

WARNINGS AND PRECAUTIONS

- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.6)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (>5% and >placebo) are (6.1):
- OAB: urinary tract infection, dysuria, urinary retention
- Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Chronic Migraine: neck pain, headache
- Spasticity: pain in extremity
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Patients receiving concomitant treatment of BOTOX and aminglycine or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX may be potentiated (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the prophylaxis of headaches in chronic migraine, treatment of OAB, detrusor overactivity associated with a neurologic condition, upper limb spasticity, and axillary hyperhidrosis; in patients under 16 years of age for treatment of cervical dystonia; and in patients under 12 years of age for treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: DISTANT SPREAD OF TOXIN EFFECT

1 INDICATIONS AND USAGE

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

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 Upper Limb Spasticity
2.6 Cervical Dystonia
2.7 Primary Axillary Hyperhidrosis
2.8 Blepharospasm
2.9 Strabismus
3 DOSEAGE FORMS AND STRENGTHS

4 CONTRAINdications

4.1 Known Hypersensitivity to Botulinum Toxin
4.2 Injection at the Injection Site(s)
4.3 Urinary Tract Infection or Urinary Retention

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products
5.2 Spread of Toxin Effect
5.3 Serious Adverse Reactions with Unapproved Use
5.4 Hypersensitivity Reactions
5.5 Pre-Existing Neuromuscular Disorders
5.6 Dysphagia and Breathing Difficulties
5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition
5.8 Neoral Exposure and Ucleration in Patients Treated with BOTOX for Blepharospasm
5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus
5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition
5.12 Urinary Tract Infections in Patients with Overactive Bladder
5.13 Urinary Retention in Patients Treated for Bladder Dysfunction
5.14 Human Albumin and Transmission of Viral Diseases

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
6.2 Immunogenicity
6.3 Post-Marketing Experience

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission
7.2 Anticholinergic Drugs
7.3 Other Botulinum Neurotoxin Products
7.4 Muscle Relaxants

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

10 OVERDOSE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)
14.2 Detrusor Overactivity associated with a Neurologic Condition
14.3 Chronic Migraine
14.4 Upper Limb Spasticity
14.5 Cervical Dystonia
14.6 Primary Axillary Hyperhidrosis
14.7 Blepharospasm
14.8 Strabismus

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, on local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

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

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

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

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

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, 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.

Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine
Table 2: BOTOX Dosing by Muscle for Chronic Migraine

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose (Number of Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis</td>
<td>20 Units divided in 4 sites</td>
</tr>
<tr>
<td>Corrugator</td>
<td>10 Units divided in 2 sites</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 Units in 1 site</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 Units divided in 6 sites</td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 Units divided in 8 sites</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 Units divided in 6 sites</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group</td>
<td>20 Units divided in 4 sites</td>
</tr>
</tbody>
</table>

Total Dose: 155 Units divided in 31 sites

- Each IM injection site = 0.1 mL = 5 Units BOTOX
- Dose distributed bilaterally

2.5 Upper Limb 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. 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

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose Total Dosage (Number of Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps Brachii</td>
<td>100 Units-200 Units divided in 4 sites</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>12.5 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>12.5 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor Digitorum Profundus</td>
<td>30 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>30 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units in 1 site</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units in 1 site</td>
</tr>
</tbody>
</table>

Figure 2: Injection Sites for Upper Limb Spasticity

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 hyper trophy, 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. 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 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 Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor’s iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Table 1). Using a 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, 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 3.

Figure 3: Injection Pattern for Primary Axillary Hyperhidrosis

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

2.8 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. Emmetropia 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 diptors: 1.25 Units for verticle muscles, 2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diptors to 50 prism diptors: 2.5 Units for horizontal muscles, 5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units for horizontal muscles, 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

Single-use, sterile 100 Units or 200 Units vacuum-dried powder 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).

### 5 WARNINGS AND PRECAUTIONS

**5.1 Lack of Interchangeability between Botulinum Toxin Products**

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see Dosage and Administration (2.1), Description (11)].

**5.2 Spread of Toxin Effect**

Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and upper limb spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX/BOTOX Cosmetic at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

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

### 5.3 Serious Adverse Reactions with Unapproved Use

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

### 5.4 Hypersensitivity Reactions

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

### 5.5 Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored closely. In a double-blind, placebo-controlled, parallel group study comparing BOTOX for blepharospasm at the recommended dose (30 Units and below), strabismus, or for axillary hyperhidrosis at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

**5.6 Dysphagia and Breathing Difficulties**

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in swallowing or breathing [see Warnings and Precautions (5.2)]. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

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

Patients with a compromised respiratory status treated with BOTOX for upper limb spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients with stable reduced pulmonary function (defined as FEV1 <40-80% of predicted value and FVC <75%), 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 4).

#### Table 4: Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 post-injection with up to two treatment cycles with BOTOX or placebo

<table>
<thead>
<tr>
<th>Week</th>
<th>15% Decrease</th>
<th>20% Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Week 12</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Differences from placebo were not statistically significant.

In 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 an ongoing 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 5).

### Table 5: 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>Timepoint</th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥15%</td>
<td>≥20%</td>
</tr>
<tr>
<td>Week 2</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>2/11 (18%)</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0/11 (0%)</td>
<td>0/11 (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%).

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, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

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

**Urinary 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 6. The duration of post-injection catheterization for those who developed urinary retention is also shown.

### Table 6: 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 200 Units (N=552)</th>
<th>Placebo (N=542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Patients Catheterizing for Urinary Retention</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>Median 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 7.

### Table 7: 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>BOTOX 100 Units (N=81)</td>
<td>Placebo (N=89)</td>
</tr>
<tr>
<td>Placebo 100 Units (N=526)</td>
<td>Placebo (N=516)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>12.3% (n=10)</td>
</tr>
</tbody>
</table>

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. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

### 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)]
- Hypersensitivity [see Contraindications (4.1) and Warnings and Precautions (5.4)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity [see Warnings and Precautions (5.10)]
- 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, injection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., 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 10 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 10: 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).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 11.

Table 11: 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></th>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX 100 Units (N=81)</td>
<td>Placebo (N=69)</td>
</tr>
<tr>
<td></td>
<td>BOTOX 100 Units (N=526)</td>
<td>Placebo (N=516)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>25 (31%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td></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 12 presents the most frequently reported adverse reactions in double-blind, placebo-controlled studies within 12 weeks of injection for detrusor overactivity associated with a neurologic condition.

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

<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>Hematuria</td>
<td>10 (4%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

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 44 weeks of exposure): 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 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.

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 13.

Table 13: 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>26 (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 spasticity appear in Table 14.

Table 14: Adverse Reactions Reported by ≥2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult 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=113)</th>
<th>BOTOX 150 Units-250 Units (N=186)</th>
<th>BOTOX &lt;150 Units (N=54)</th>
<th>Placebo (N=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorder</td>
<td>3 (3%)</td>
<td>2 (1%)</td>
<td>1 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>4 (3%)</td>
<td>2 (1%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>4 (3%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (6%)</td>
<td>5 (9%)</td>
<td>8 (4%)</td>
<td></td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10 (5%)</td>
<td>0</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>7 (6%)</td>
<td>5 (9%)</td>
<td>8 (4%)</td>
<td></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.
Cervical Dystonia

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%). Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertension, soreness at injection site, asthma, oral dryness, speech disorder, fever, nausées, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dysphoria have been reported. Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles [see Warnings and Precautions (5.2, 5.6)].

The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea [see Warnings and Precautions (5.2, 5.6)]. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms [see Warnings and Precautions (5.6)]. Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of BOTOX for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis

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

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

Blepharospasm

In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured BOTOX, the most frequently reported adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%). Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

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

Strabismus

Extracocular muscles adjacent to the injection site can be affected, causing vertical deviation, strabismus with higher doses of BOTOX. The incidence rates of these adverse effects in 2059 adults who received a total of 3650 injections for horizontal strabismus was 17%. The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

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

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin.

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%), no patients among 406 migraine patients, no patients among 615 overactive bladder patients, and no patients among 475 detrusor overactivity associated with a neurologic condition patients with analyzed specimens developed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to BOTOX in a mouse protection assay. The results of these tests are 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 neutralizing activity to BOTOX with the incidence of antibodies to other products may be misleading.

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; bronchial plexopathy; dermatitis/pigment atrophy; diarrhea; hyperdriasis; hypoaesthetic; hypoesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis poikiloderma; and poikiloderma 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

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. BOTOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats beginning 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 0.7 times the average high human dose for upper limb spasticity of 360 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 average high human dose 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 3 times the average high human dose based on Units/kg.

8.3 Nursing Mothers

It is not known whether BOTOX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX is administered to a nursing woman.

8.4 Pediatric Use

Bledder 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.

Spasticity

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

Axillary Hyperhidrosis

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

Cervical Dystonia

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.
Botox is a medication that is used to treat various conditions, including overactive bladder (OAB), by weakening the muscles in the bladder and related areas. It is typically used in patients who have symptoms of urgency, frequency, and/or urge incontinence. Botox contains a neurotoxin derived from Clostridium botulinum type A, which when injected into the bladder, temporarily inhibits certain nerve functions.

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 and cannot be compared to nor converted into Units of any other botulinum toxin or any vehicle, dilution scheme, and laboratory protocols. Units of biological activity of Botox 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/nanogram of neurotoxin protein complex.

**10 OVERTOXITY**

Excessive doses of Botox (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Symptoms of overdose are likely 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]].

**14 CLINICAL STUDIES**

14.1 Overtactive Bladder (OAB)

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for Botox 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 16 and 17, and Figures 4 and 5.
Table 16: 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><strong>Daily Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>-1.6</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-2.8</td>
<td>-1.0</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-2.5</td>
<td>-0.9</td>
<td>-1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Volume Voided per Micturition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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.
† LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.
** Primary timepoint
a Primary variable
b Secondary variable

Table 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><strong>Daily Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>-1.6</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-3.1</td>
<td>-1.3</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-3.0</td>
<td>-1.1</td>
<td>-1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Volume Voided per Micturition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>12.0</td>
<td>11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-2.3</td>
<td>-0.6</td>
<td>-1.7 (-2.2, -1.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.
† LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.
** Primary timepoint
a Primary variable
b Secondary variable

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 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 Tables 18 and 19, and Figures 6 and 7.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.
Table 18: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) 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>Weekly Frequency of Urinary Incontinence Episodes*</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</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>Maximum Cystometric Capacity (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>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (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

a Primary endpoint

b Secondary endpoint

Table 19: 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>Weekly Frequency of Urinary Incontinence Episodes*</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>Maximum Cystometric Capacity (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>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (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

a Primary endpoint

b Secondary endpoint

The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 296-337 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).

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 20).

Table 20: 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>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 8), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 9), compared to placebo-treated patients.
The primary efficacy variable was wrist flexor muscle tone at week 6, as measured by the Ashworth Scale, but allows for half-point increments. 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 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 23).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle 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 22.

Table 22: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

<table>
<thead>
<tr>
<th>Total Dose</th>
<th>Muscles Injected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX low dose</td>
</tr>
<tr>
<td></td>
<td>(90 Units)</td>
</tr>
<tr>
<td></td>
<td>BOTOX mid dose</td>
</tr>
<tr>
<td></td>
<td>(180 Units)</td>
</tr>
<tr>
<td></td>
<td>BOTOX high dose</td>
</tr>
<tr>
<td></td>
<td>(360 Units)</td>
</tr>
<tr>
<td></td>
<td>Volume (mL) per site</td>
</tr>
<tr>
<td></td>
<td>Injection Sites (n)</td>
</tr>
<tr>
<td>Wrist</td>
<td>Flexor Carpi Radialis</td>
</tr>
<tr>
<td></td>
<td>Flexor Carpi Ulnaris</td>
</tr>
<tr>
<td>Finger</td>
<td>Flexor Digitorum Profundus</td>
</tr>
<tr>
<td></td>
<td>Flexor Digitorum Sublimis</td>
</tr>
<tr>
<td>Elbow</td>
<td>Biceps Brachii</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 24.

Table 23: Study Medication Dose and Injection Sites in Study 2 and Study 3

<table>
<thead>
<tr>
<th>Injection Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX low dose (90 Units) (N=21)</td>
</tr>
<tr>
<td>BOTOX mid dose (180 Units) (N=23)</td>
</tr>
<tr>
<td>BOTOX high dose (360 Units) (N=21)</td>
</tr>
<tr>
<td>Placebo (N=26)</td>
</tr>
<tr>
<td>Volume (mL) per site</td>
</tr>
<tr>
<td>Injection Sites (n)</td>
</tr>
<tr>
<td>Wrist</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Finger</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Elbow</td>
</tr>
</tbody>
</table>

The primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo (p≤0.05)
††Dose of BOTOX injected into biceps brachii muscle

14.4 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 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 21). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 21: 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</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>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</td>
<td>1</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>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</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>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
†† Significantly different from placebo (p≤0.05)
†††Dose of BOTOX injected into biceps brachii muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a clinical measure of the force required to move a joint (i.e., improvement in spasticity). Possible scores range from 0 to 4:
1 = Slight increase in muscle tone, giving a ‘catch’ when the limb was moved in flexion or extension (mild)
2 = More marked increase in muscle tone but affected limb is easily flexed (moderate)
3 = Considerable increase in muscle tone - passive movement difficult (severe)
4 = Limb rigid in flexion or extension (very severe).
In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone were shown in Table 25.

Table 25: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>BOTOX Dose (Units)</th>
<th>Placebo (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thumb Adductor Pollicis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose (90)</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>Mid dose (180)</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>High dose (360)</td>
<td>-1.5*</td>
<td>-0.5</td>
</tr>
<tr>
<td>Median Change from Baseline on ELBOW Flexor Muscle Tone on the Ashworth Scale†††</td>
<td>1.0 0.0 2.0* 0.0</td>
<td>Placebo (N=14)</td>
</tr>
<tr>
<td>Finger Flexor Pollicis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose (40)</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>Mid dose (80)</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>High dose (120)</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>Median Change from Baseline on THUMB Flexor Muscle Tone on the Ashworth Scale†††</td>
<td>1.0 0.0 2.0* 0.0</td>
<td>Placebo (N=9)</td>
</tr>
</tbody>
</table>

Table 26: Study Medication Dose and Injection Sites in Studies 4 and 5

<table>
<thead>
<tr>
<th>Study</th>
<th>Study 4</th>
<th>Study 5</th>
<th>Number of Injection Sites for Studies 4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BOTOX (Units)</td>
<td>Volume (mL)</td>
<td>BOTOX low dose (Units)</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>0.4</td>
<td>15 20 0.3 0.4 1</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
<td>15 20 0.3 0.4 1</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
<td>15 20 0.3 0.4 1</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 and overall treatment response by Physician Global Assessment at week 6 are presented in Table 27.

Table 27: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>BOTOX (N=68)</th>
<th>Placebo (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline on THUMB Flexor Muscle Tone on the Ashworth Scale†††</td>
<td>-1.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>Median Physician Global Assessment of Response to Treatment†</td>
<td>2.0*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 28: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>BOTOX low dose (30 Units)</th>
<th>Placebo low dose (N=9)</th>
<th>BOTOX high dose (40 Units)</th>
<th>Placebo high dose (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline on THUMB Flexor Muscle Tone on the modified Ashworth Scale†††</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-0.5*</td>
<td>0.0</td>
</tr>
<tr>
<td>Median change from Baseline on Clinical Global Impression Score by Physician†</td>
<td>1.0</td>
<td>0.0</td>
<td>2.0*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1† †† Secondary endpoints at Week 6
2†† Secondary endpoints at Week 6
3 Significantly different from placebo (p<0.005)
4 Significantly different from placebo (p≤0.010)
5 ††† BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

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 allows 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 29.

Table 29: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>BOTOX (N=88)</th>
<th>Placebo (N=82)</th>
<th>95% CI on Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CDSS</td>
<td>9.3</td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>Change in CDSS at Week 6</td>
<td>-0.3</td>
<td>-1.3</td>
<td>(-2.3, 0.3)††</td>
</tr>
<tr>
<td>% Patients with Any Improvement on Physician Global Assessment</td>
<td>31%</td>
<td>51%</td>
<td>(5%, 34%)†††</td>
</tr>
<tr>
<td>Pain Intensity Baseline</td>
<td>1.8</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Pain Intensity at Week 6</td>
<td>-0.1</td>
<td>-0.4</td>
<td>(-0.7, -0.2)†</td>
</tr>
<tr>
<td>Pain Frequency Baseline</td>
<td>1.9</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Change in Pain Frequency at Week 6</td>
<td>-0.0</td>
<td>-0.3</td>
<td>(-0.5, -0.0)†</td>
</tr>
</tbody>
</table>

†† Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
††† 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.
† Confidence intervals are based on the t-distribution.

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

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 30. The total dose and muscles selected were tailored to meet individual patient needs.
Table 30: 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>Sternocleidomastoid</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 persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = "underarm sweating is never noticeable and never interferes with my daily activities"; 2 = "underarm sweating is noticeable and interferes with my daily activities"; 3 = "underarm sweating is intolerable and always interferes with my daily activities"; and 4 = "underarm sweating is intolerable and always interferes with my daily activities". A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

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

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

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group (p<0.001), but was not significantly different between the two BOTOX doses (see Table 31).

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 patients 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 31: 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 50-placebo (95% CI)</th>
<th>BOTOX 75-placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDSS Score change ≥2 (n)*</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% (26.1, 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 dipters or less when evaluated six months or more following injection.

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes: 100 Units, 200 Units. NDC 0023-1145-01, NDC 0023-3921-02.

Unopened vials of BOTOX should be stored in a refrigerator (2° to 8°C) for up to 36 months. Do not use after the expiration date on the vial. Administer BOTOX within 24 hours of reconstitution; during this period reconstituted BOTOX should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX should be clear, colorless, and free of particulate matter.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) before starting use of BOTOX.

Swallowing, Speaking or Breathing Difficulties

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.

Ability to Operate Machinery or Vehicles

Advise patients that if loss of strength, muscle weakness, blurred vision, or drooping eyelids occurs, they should avoid driving a car or engaging in other potentially hazardous activities.

Voiding Symptoms after Bladder Injections

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

Read the Medication Guide that comes with BOTOX or BOTOX Cosmetic before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

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:
1. Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with BOTOX or BOTOX Cosmetic.

- People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with BOTOX or BOTOX Cosmetic.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving BOTOX or BOTOX Cosmetic have the highest risk of getting these problems.

2. Spread of toxin effects. In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

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

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

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

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:
- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder 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 with 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 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 the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat c...
Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. 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 should I take 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 taking BOTOX or BOTOX Cosmetic?
BOTOX and BOTOX Cosmetic may cause loss of strength or general muscle weakness, or vision problems 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.
- 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: botulinum toxin type A
Inactive ingredients: human albumin and sodium chloride

Revised: 08/2015
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc.
2525 Dupont Dr.
Irvine, CA 92612
© 2015 Allergan. All rights reserved.
® marks owned by Allergan, Inc.
Patented. See: www.allergan.com/products/patent_notices
Myobloc® is a registered trademark of Solstice Neurosciences, Inc.
Dysport® is a registered trademark of Ipsen Biopharm Limited Company.
Xeomin® is a registered trademark of Merz Pharma GmbH & Co KGaA.