NAVIGATING THE BOTOX® REIMBURSEMENT LANDSCAPE

BOTOX® (onabotulinumtoxinA) for appropriate patients

**Indications**

**Chronic Migraine**

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

**Important Limitations**

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

**Spasticity:**

**Upper Limb Spasticity**

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

**Lower Limb Spasticity**

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

**Important Limitations**

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

**IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING**

**WARNING: DISTANT SPREAD OF TOXIN EFFECT**

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses.

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

This module is intended to provide insight that may streamline BOTOX® (onabotulinumtoxinA) reimbursement processes and help ensure that your BOTOX® patients have continued access to treatment per your provider’s recommendation. For each member of the practice’s treatment team who plays a role in the BOTOX® patient journey, understanding what steps are required for treatment approvals, correct billing, and claims reconciliation is important to both the patient and the practice, by helping patients receive timely treatment and making sure that the practice is appropriately reimbursed.

Overview

For anyone within a practice involved in the journey of a BOTOX® patient, understanding and navigating the steps required for reimbursement purposes is particularly important. While the provider(s) are responsible for all of the clinical decisions around BOTOX® treatment, the reimbursement information provided in this module may help you to gain even greater familiarity with ways in which you can best support patients from the start of their journey through their ongoing treatment with BOTOX®.

Indications (continued)

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

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

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

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

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

Please see additional Important Safety Information about BOTOX® on following pages.
Securing Treatment Approvals for Your BOTOX® (onabotulinumtoxinA) Patient

Understanding the Payer Landscape

In addition to your practice’s BOTOX® patient population, many of the patients that your provider treats who have active health insurance, will fall into one of the following, two primary types of payers (insurance companies and health plans) – government and commercial.

- **Government Plans**: Payers include Medicare, Medicaid, Veteran’s Administration and active military, state health insurance exchanges, and others

- **Commercial Plans**: Payers include managed care organizations (MCOs), pharmacy benefit managers (PBMs), and employers

It is important to understand the top local payers who cover the majority of your BOTOX® patients, as each one may have different requirements that must be met before treatment may begin.

Most Medicare carriers and some Medicaid and commercial payers, have a medical policy specific to BOTOX®. This medical policy may include specific details that must be documented clearly in the patient’s chart notes to show that your provider considers BOTOX® to be medically necessary.

Who are our top payers?

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**IMPORTANT SAFETY INFORMATION (continued)**

**CONTRAINDICATIONS**

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

**WARNINGS AND PRECAUTIONS**

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.

Please see additional Important Safety Information about BOTOX® on following pages.
Verifying Your BOTOX® (onabotulinumtoxinA) Patient’s Benefits

As with all patients treated in your practice, it is important to confirm that the patients your provider intends to treat with BOTOX® have active health insurance, and that their health plan includes coverage for BOTOX® (excluding patients who are self-pay). Patient insurance is subject to change throughout the year and therefore regular re-verification of the patient’s insurance benefits prior to each planned treatment is key.

During the benefit verification process for a new or repeat BOTOX® patient, it may be helpful to understand the following:

- **Prior Authorization (PA) Requirements:** Whether the treatment and/or drug needs to be pre-approved
- **BOTOX® Acquisition Guidelines:** Whether the practice needs to buy the drug from Allergan or use a specialty pharmacy (SPP)
- **Treatment Limits:** For example, the number of treatments and dosing a patient is eligible to receive
- **Patient Financial Responsibility:** Whether the patient will have to pay something toward the cost of the drug and/or the procedure visit
  - **Deductible:** A deductible is the amount the patient pays for health care services before the payer begins to share expenses.
  - **Co-payment:** A method of cost-sharing used by payers that is a set amount the patient pays for an encounter that is determined by the patient’s type of plan.
  - **Co-Insurance:** A method of cost-sharing used by payers that requires the patient to pay a percentage of the cost of the encounter.

Notes

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Spread of Toxin Effect
See Boxed Warning.

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

Please see additional Important Safety Information about BOTOX® on following pages.
Securing BOTOX® (onabotulinumtoxinA) Treatment Approvals

Many payers, though not all, require providers to follow a pre-approval process prior to injecting a patient with BOTOX®. This is usually referred to as prior authorization or a “PA”.

The payer’s intent in requiring a prior authorization is to ensure that a drug is used according to their medical policy. Payers may have their own specific prior authorization form that will need to be completed. Some may also require a separate Letter of Medical Necessity (LOMN) to be submitted, and others may ask for the patient’s clinical notes to be submitted along with PA request/LOMN.

If a Letter of Medical Necessity is required, your provider will typically need to include the following six key elements:

1. Documentation of other medical services that represent a significant expense.
2. Detail of the impact of the diagnosis on the patient.
3. Inclusion of appropriate medical literature on the diagnosis as it relates to the approved indications.
4. Explanation of the physician’s experience and training using BOTOX®
5. Explanation the BOTOX® procedure and anticipated outcome
6. Documentation of patient history

Please note; the information needed by the health plan may vary by type of condition being proposed for treatment with BOTOX®.

Notes

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

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.

Please see additional Important Safety Information about BOTOX® on following pages.
Successful treatment approvals for BOTOX® (onabotulinumtoxinA) rely on accurate and detailed provider documentation to support the patient’s clinical need for BOTOX® including, but not limited to, the following:

- Evidence of medical necessity to show that BOTOX® treatment is appropriate for the patient.
- A covered diagnosis (ICD-10-CM code).
- The relevant procedure (CPT®) code to describe the injections/areas of the body the provider intends to treat with BOTOX®.
- A list of traditional therapies that have been tried and failed.
- An injection treatment plan (including injection site(s) and the amount of BOTOX® units the provider will inject into the patient, which can vary based on the disease state).

Payers vary in the documentation they require in order to approve a prior authorization for patients and the specific details needed may change over time. Using prior authorization checklists and templates to capture this documentation, either in printed form or within the practice’s electronic medical record system, can help capture required information in a consistent manner. Your Allergan representative can provide samples of checklists that may be helpful for you and your providers.

When obtaining a prior authorization, it is important to allow adequate time for approvals before the planned BOTOX® injection and set realistic expectations with your injector and patient regarding approval timelines (which may vary by payer from a few days, to two to three weeks or longer). This will help to prevent last-minute treatment delays and help ensure that reimbursement claims can be made appropriately following injection.

Notes

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**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.

Please see additional Important Safety Information about BOTOX® on following pages.
Ordering BOTOX® (onabotulinumtoxinA): Drug Acquisition Options

Once you have received approval from the payer on behalf of your BOTOX® patient, it will be time to order BOTOX® for his or her injection appointment. There are two primary methods for acquiring BOTOX® for your patient:

1. **Buy and Bill:** Practices may purchase BOTOX® from Allergan and then bill the health plan when the vial is used. With this method, the practice keeps inventory and carries the financial responsibility for BOTOX®. The following may be helpful in obtaining BOTOX® vials through the buy and bill process:
   - To order BOTOX® by phone, call 1-800-44-BOTOX, and then select option 1.
   - BOTOX® can also be ordered by a registered user at www.allergandirect.com
   - BOTOX® orders are shipped overnight with the exception of a Friday delivery.

2. **Specialty Pharmacy Provider (SPPs):** SPPs are an entire class of providers that exist primarily to distribute and dispense specialty drugs. Some health plans require that BOTOX® is obtained through this method, while others allow the provider to choose either SPP or buy and bill. When SPP is used, the cost of the drug is billed by the SPP directly to the health plan. With this method, the SPP carries the financial responsibility for the BOTOX® vial instead of the practice.

There are several factors that may determine whether a practice chooses to buy and bill BOTOX® from Allergan or have an SPP provide BOTOX® for a designated patient.

- Medicare typically requires the provider to buy and bill BOTOX® since it is considered a Part B drug. Part B drugs are administered by a healthcare provider.

- Commercial plans can vary in terms of an SPP option. The patient's health plan will specify if SPP is required and whether a particular SPP needs to be used for the supply of the drug. Others may allow free provider choice of the SPP to be used for acquiring BOTOX®. Many commercial plans do not mandate use of SPP, allowing providers to buy and bill the product directly.

If you play a role in the treatment approval process, it will be important for you to know and understand the differences between health plans to secure timely approvals and help ensure that the BOTOX® vials are ordered according to payer and your provider’s direction.

How does our practice acquire BOTOX® for our patients?

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders**
 Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX® (see Warnings and Precautions).

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

Once the BOTOX® (onabotulinumtoxinA) ordered for your patient has arrived at your practice, it is important to track the vial. Monitoring BOTOX® inventory coming in on a regular basis can help ensure drug availability at the time of service, aid in the management of the ordering cycle and associated costs, and avoid unnecessary inventory or product expiration.

Practices can effectively manage BOTOX® inventory using the following tips:

- Implement an ordering system (e.g., weekly, bi-weekly) based on practice needs.
- Monitor orders and shipments received and document in a logbook.
- Follow proper storage and handling of BOTOX®.
- Perform a monthly reconciliation of inventory.
- Use a logbook to also help reconcile the amount purchased versus the amount used, billed, and paid for by insurance and patient.

As mentioned previously, some commercial carriers may require that that the product is ordered from a Specialty Pharmacy Provider (SPP). BOTOX® received from a SPP should be kept separately from BOTOX® purchased directly from Allergan, as a vial shipped via a SPP is designated for a specific patient.

## Notes

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Dysphagia and Breathing Difficulties**

Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see Boxed Warning).

Please see additional Important Safety Information about BOTOX® on following pages.
BOTOX® (onabotulinumtoxinA) Procedure Day

Patient Collection Processes

Providing your patient with his or her BOTOX® financial responsibility prior to the injection visit is ideal so that out-of-pocket cost can be gathered at the time of the appointment. Patients are more likely to pay before they are treated rather than after. Practices may also choose to call the patient prior to the office visit to convey expected out-of-pocket costs for BOTOX®.

Documenting the BOTOX® Procedure

It is important for the provider to record the BOTOX® injection details including:

- Date of service
- Frequency of injections
- Wastage
- Clinical effectiveness of BOTOX®
- Clinical rationale of electromyography (EMG), if applicable
- Muscles injected, sites per muscle, and dosing per site

Notes

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Pulmonary Effects of BOTOX® in Patients With Compromised Respiratory Status Treated for Spasticity
Patients with compromised respiratory status treated with BOTOX® for spasticity or detrusor overactivity associated with a neurologic condition should be monitored closely.

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.

Please see additional Important Safety Information about BOTOX® on following pages.
Provider Billing for BOTOX® (onabotulinumtoxinA) Treatments

Billing/Claim Submission

Once your BOTOX® patient has been injected, your role may involve helping your provider to bill the payer for services rendered. It is important to follow the payer’s billing/coding guidelines for both the procedure and the drug. The relevant codes that may typically be included in a BOTOX® treatment claim will include the following:

• **ICD-10-CM:** Diagnosis code

• **CPT® code:** Procedure code, including injection guidance code where used by your provider
  - Only certain CPT® codes can be matched with specific diagnosis codes so it is important for your provider to indicate the correct pairing to be used for the patient encounter

• **J-Code:** The drug component of the patient encounter
  - This will only be included for those patients where the drug has been obtained through the buy and bill method, as SPP-provided drug will be billed directly to the health plan.

• **National Drug Code (NDC):** A unique product identifier used in the United States for drugs intended for human use.

• **Modifiers:** Signifies an alteration has occurred either to the procedure or the use of the drug

For buy and bill J-Code claims, the most frequent “watch outs” to be mindful of are as follows:

• **Accurate coding for BOTOX®**
  - Payers require the drug to be billed by the unit (not by the vial)
  - Example: J0585 – INJECTION, ONABOTULINUMTOXINA, 200 UNITS

• **Billing for unavoidable wastage:**
  - Each vial BOTOX® is approved for single-patient use and, therefore, most payers will reimburse for any remaining units left in the vial and that will be discarded after the provider has injected the patient.
  - Payers vary in how they require wastage to be recorded and billed so it is important to know, and clearly follow, these guidelines which may include the use of a J-Code Modifier. For all patients, it is good practice for providers to document in the patient’s medical record the exact amount of BOTOX® injected and any unavoidable wastage discarded.

Notes

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

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.

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

As with all patient encounters in your practice, BOTOX® (onabotulinumtoxinA) claims should also be monitored regularly to help both the practice and patients remain on track with treatment and appropriate reimbursement. Your role, or the role of another member of the practice team, may involve comparing claims submitted with payments received from the health plans. This is an important part of the overall billing process which aids in:

- Collection of accurate patient co-insurance amounts based on amounts received from the health plan.
- Identification of claims that have been denied, either in whole or partly, so that prompt decisions can be made by your provider to appeal.
- Understanding changing payer requirements for appropriate billing that may or may not be included in updated medical policy (i.e., use of drug wastage modifiers).

Claims Appeal

At times, you many need to appeal a claim denial or address other issues with a claim. In managing this process it may be helpful to:

- Understand the required documentation and forms to file when appealing.
- Track the length of the appeals window.
- Maintain a file of denial reasons to help identify payer trends.
- Complete a Letter of Medical Necessity (LOMN) to be used to appeal underpaid or denied claims. A LOMN documents a patient’s history and provides an explanation of why the proposed services rendered are necessary based on the patient’s medical diagnosis.

Notes

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
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 251-360 Units total dose) compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX® (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX® (2% at 300 Units to 400 Units total dose), compared to placebo (1%).

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.

Please see additional Important Safety Information about BOTOX® on following pages.
Allergan Financial Support for Your BOTOX® (onabotulinumtoxinA) Patients

As patients may face increasing out-of-pocket costs due to high deductibles and higher co-insurance percentages, you may consider advising patients of potential options for financial assistance related to BOTOX® treatment including:

- **BOTOX® Savings Card**: For commercially insured patients receiving BOTOX® for a therapeutic use (who may not be enrolled in, or eligible for Medicare, Medicaid, or any other federal or state government health program). This card can only be used in a hospital, doctor's office, or pharmacy.

- **BOTOX PATIENT ASSISTANCE® Program**: Dedicated to helping financially eligible patients receive BOTOX® for any of the therapeutic indications. It provides BOTOX® at no cost for financially eligible patients.

- **Cervical Dystonia Fund**: Helps financially eligible patients with cervical dystonia receive treatment. It is open to patients with all types of insurance including those with Medicare, and is administered by the National Organization for Rare Disorders (NORD), which independently determines patient eligibility.

**Follow-up/Documentation Protocols**

Patients who are treated with BOTOX® therapy should be evaluated at physician directed intervals to assess treatment results. These follow-ups may be conducted by the physician or relevant staff per the physician direction, and the practice should be sure that the documentation of treatment results meet payer criteria and guidelines to support ongoing treatment as directed by the provider. Patients should also be educated on follow-up expectations so they are prepared to provide relevant treatment results to the provider.

**Notes**

**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS**

The following adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning); Serious Adverse Reactions with Unapproved Use (see Warnings and Precautions); Hypersensitivity Reactions (see Contraindications and Warnings and Precautions); Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders (see Warnings and Precautions); Dysphagia and Breathing Difficulties (see Warnings and Precautions); Pulmonary Effects of BOTOX® in Patients with Compromised Respiratory Status Treated for Spasticity (see Warnings and Precautions); Corneal Exposure and Ulceration in Patients Treated with BOTOX® for Blepharospasm (see Warnings and Precautions); Retrobulbar Hemorrhages in Patients Treated with BOTOX® for Strabismus (see Warnings and Precautions); and Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity (see Warnings and Precautions).

Please see additional Important Safety Information about BOTOX® on following pages.
Leveraging the Treatment Team

The BOTOX® (onabotulinumtoxinA) treatment team is comprised of staff members who vary within practices. Therefore, it is important to identify relevant team members within your own practice and assess his or her impact in navigating the BOTOX® reimbursement landscape, as each person plays an important role in ensuring appropriate patients have access to care (please see the following table as an example).

<table>
<thead>
<tr>
<th>ROLE</th>
<th>POTENTIAL RESPONSIBILITY</th>
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<tbody>
<tr>
<td>Front Desk/Check-Out Staff</td>
<td>• Eligibility check&lt;br&gt;• Notify patient of financial responsibility&lt;br&gt;• Educate patient in financial assistance options&lt;br&gt;• Patient Collection Processes</td>
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<tr>
<td>Clinical Staff</td>
<td>• Documentation&lt;br&gt;• Insurance verification (IV) and prior authorization (PA) process&lt;br&gt;• Drug acquisition&lt;br&gt;• Follow-up documentation&lt;br&gt;• Inventory management&lt;br&gt;• Educate patient in financial assistance options</td>
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<td>Providers</td>
<td>• Documentation&lt;br&gt;• Coding&lt;br&gt;• Follow-up documentation&lt;br&gt;• Writing a LOMN</td>
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<tr>
<td>Administrative Department</td>
<td>• Claim submission&lt;br&gt;• Inventory management&lt;br&gt;• Claims reconciliation&lt;br&gt;• Drug acquisition&lt;br&gt;• Insurance verification (IV) and prior authorization (PA)&lt;br&gt;• Patient collection processes</td>
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<tr>
<td>BOTOX® Patient Navigator</td>
<td>The BOTOX® Patient Navigator can perform a number of these responsibilities, or ensure there is a process in place that connects the elements of the reimbursement process.</td>
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My roles and responsibilities to discuss with my supervisor:

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Chronic Migraine
The most frequently reported adverse reactions following injection of BOTOX® for chronic migraine include neck pain (9%), headache (5%), eyelid ptosis (4%), migraine (4%), muscular weakness (4%), musculoskeletal stiffness (4%), bronchitis (3%), injection-site pain (3%), musculoskeletal pain (3%), myalgia (3%), facial paresis (2%), hypertension (2%), and muscle spasms (2%).

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

The following list provides examples of the type resources that Allergan can provide to assist your practice in Navigating the BOTOX® Reimbursement Landscape. Ask your Neuroscience Business Practice Specialist (NBPS) or your Neuroscience Sales Specialist (NSS) for the most up-to-date resource(s) for your practice:

- Prior Authorization Checklists
- Chart Documentation Treatment Records
- Billing and Coding Reference Tools
- *ICD-10 CM* Crosswalk
- Sample Claim Forms
- Specialty Pharmacy Provider Resources
- Payer Policy Grids

Process Map

1. Patient is identified for BOTOX® (onabotulinumtoxinA) treatment
2. Secure treatment approval for the BOTOX® patient
3. Order BOTOX®
4. Maintain inventory
5. Collect patient financial responsibility on the injection day
6. Procedure documentation on the injection day
7. Claim submission
8. Receipt of payment from insurance company
9. Reconcile claims
10. Follow-up documentation
11. Collect outstanding patient balance (if any) prior to next injection

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS (continued)

Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® for upper limb spasticity include pain in extremity, muscle weakness, fatigue, nausea, and bronchitis.

Please see additional Important Safety Information about BOTOX® on following page.
IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS (continued)

Lower Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX® (onabotulinumtoxinA) for lower limb spasticity include arthralgia, back pain, myalgia, upper respiratory tract infection, and injection site pain.

Cervical Dystonia
The most frequently reported adverse reactions following injection of BOTOX® for cervical dystonia include dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Blepharospasm
The most frequently reported adverse reactions following injection of BOTOX® for blepharospasm include ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Strabismus
The most frequently reported adverse events following injection of BOTOX® for strabismus include ptosis (15.7%) and vertical deviation (16.9%).

Primary Axillary Hyperhidrosis
The most frequently reported adverse events (3%-10% of adult patients) following injection of BOTOX® for severe primary axillary hyperhidrosis include injection-site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

Post Marketing Experience
There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. 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.

DRUG INTERACTIONS
Co-administration of BOTOX® and amino glycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. 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. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX®.

Please see accompanying full Prescribing Information including Boxed Warning and Medication Guide.
Navigating the BOTOX® (onabotulinumtoxinA) Reimbursement Landscape

Module Quiz

For each of the following, decide whether the statement is True or False.

1. It is important to understand the top local payers who cover the majority of your BOTOX® patients, as each one may have different requirements that must be met before treatment may begin.

2. Patient insurance never changes throughout the year and therefore regular re-verification of the patient’s insurance benefits prior to each planned treatment is not important.

3. It is not important to complete a prior authorization for BOTOX® injections.

4. Successful treatment approvals for BOTOX® rely on accurate and detailed provider documentation to support the patient’s clinical need for BOTOX®.

5. Allergan provides no options for financial assistance related to BOTOX® treatment.
Navigating the BOTOX® (onabotulinumtoxinA) Reimbursement Landscape

Module Quiz: Answer Key

1. True
2. False
3. False
4. True
5. False
BOTOX® Patient Navigator Program

Certificate of Completion

This certificate is to be presented to

For the successful completion of the NAVIGATING THE BOTOX® REIMBURSEMENT LANDSCAPE module

Please see accompanying full Prescribing Information including Boxed Warning and Medication Guide.

Completion Date
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 symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. (5.2)

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1.2)
- Treatment of spasticity in adult patients (1.3)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)
- Treatment of strabismus in patients ≥12 years of age (1.6)

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

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

DOSE AND ADMINISTRATION

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

See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)

Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)

Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)

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

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

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

Cervical Dystonia: Base dosing on the patient’s head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naive patients (2.6)

Full Prescribing Information: Contents

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

Dosage and Administration

1.012016

01/2016

01/2016

01/2016

Recent Major Changes

DOSAGE 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)

Injection at the proposed injection site (4.2)

Contraindications: 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 spasticity (5.10)

Urinary tract infections or urinary retention in patients treated for OAB (5.12)

Urinary tract infections 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 aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents, or muscle relaxants, should be observed closely because the effect of BOTOX may be potentiated (7)

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, 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: 01/2016
2 DOSAGE AND ADMINISTRATION

1.3 Spasticity

migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

Important limitations

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

BOTOX is indicated for the treatment of spasticity and at lower doses.

reported at doses comparable to those used to treat cervical dystonia and spasticity at lower doses. [See Warnings and Precautions (5.2)]

1 INDICATIONS AND USAGE

1.1 Bladder Dysfunction

Overactive Bladder

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

Detrusor Overactivity associated with a Neurologic Condition

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

1.2 Chronic Migraine

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

Important limitations

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

1.3 Spasticity

Upper Limb Spasticity

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

6 ADVERSE REACTIONS

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6.2 Immunogenicity

6.3 Post-Marketing Experience

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7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

7.2 Anticholinergic Drugs

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7.4 Muscle Relaxants

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14.2 Detrusor Overactivity associated with a Neurologic Condition

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14.6 Primary Axillary Hyperhidrosis

14.7 Blepharospasm

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16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3 month interval.

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

2.2 Preparation and Dilution Technique

Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (see Table 1, or for specific instructions for detrusor overactivity associated with a neurologic condition see Section 2.3), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 48 hours after reconstitution. During this time period, reconstituted BOTOX should be stored in a refrigerator (2° to 8°C).

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

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

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

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

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

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

2.3 Bladder Dysfunction

General

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

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

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

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

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

200 Unit Vial of BOTOX

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

100 Unit Vial of BOTOX

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

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

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

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

Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity associated with a Neurologic Condition
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 dose 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>Head/Neck Area</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>
<tr>
<td>Total Dose:</td>
<td>155 Units divided in 31 sites</td>
</tr>
</tbody>
</table>

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

2.5 Spasticity

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

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

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

1 Upper Limb Spasticity

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 3 and Figure 1) 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 Digerotor Profundus</td>
<td>30 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor Digerotor 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>

Table 4: BOTOX Dosing by Muscle for Lower Limb Spasticity

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose Total Dosage (Number of Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius medial head</td>
<td>75 Units divided in 3 sites</td>
</tr>
<tr>
<td>Gastrocnemius lateral head</td>
<td>75 Units divided in 3 sites</td>
</tr>
<tr>
<td>Soleus</td>
<td>75 Units divided in 3 sites</td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td>75 Units divided in 3 sites</td>
</tr>
<tr>
<td>Flexor hallucis longus</td>
<td>50 Units divided in 2 sites</td>
</tr>
<tr>
<td>Flexor digeternum longus</td>
<td>50 Units divided in 2 sites</td>
</tr>
</tbody>
</table>

Figure 2: Injection Sites for Upper Limb Spasticity

Lower Limb Spasticity

The recommended dose for treating lower limb spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see Table 4 and Figure 3).

Figure 3: Injection Sites for Lower Limb Spasticity
2.6 Cervical Dystonia
A double-blind, placebo-controlled study enrolled patients who had extended histories of receiving and tolerating BOTOX injections, with prior individualized adjustment of dose. The mean BOTOX dose administered to patients in this study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The BOTOX dose was divided among the affected muscles. [see Clinical Studies (14.3)]

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of BOTOX should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia [see Warnings and Precautions (5.2, 5.5, 5.6)].

The 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 extracocular 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 motion to stabilize the alignment.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS
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 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 anesthesia, 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 spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

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

5.3 Serious Adverse Reactions with Unapproved Use

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

5.4 Hypersensitivity Reactions

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

5.5 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysphasia, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX [see Warnings and Precautions (5.6)].

5.6 Dysphagia and Breathing Difficulties

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing [see Warnings and Precautions (5.2)].

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)].

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

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely in a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV1, 40-80% of predicted value and FEV1/FVC ≤ 0.75), 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 5].

Table 5: 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></th>
<th>BOTOX 360 Units</th>
<th>BOTOX 240 Units</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15%</td>
<td>≥20%</td>
<td>≥15%</td>
<td>≥20%</td>
</tr>
<tr>
<td>Week 1</td>
<td>4%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 12</td>
<td>10%</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Differences from placebo were not statistically significant in spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo [see Warnings and Precautions (5.10)].

In 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 Forcd Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 6).

Table 6: Number and percent of patients experiencing at least a 15% or 20% decrease in FVC from baseline at Week 2, 6, 12 post-injection with BOTOX or placebo

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15%</td>
<td>≥20%</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>0/12 (0%)</td>
<td>0/11 (9%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>2/11 (18%)</td>
<td>0/11 (0%)</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; 6% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

5.11 Autonomic Dysreflexia in Patients Treated for Detr usor 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 for patients with overactive bladder and detrusor overactivity associated with a neurologic condition who received BOTOX or placebo injections.

Overactive Bladder

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with BOTOX or placebo is shown in Table 7. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 7: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials in OAB

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BOTOX 100 Units (N=552)</th>
<th>Placebo (N=542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Patients Catheterizing for Urinary Retention</td>
<td>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 8.

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)]
- Serious Adverse Reactions with Unapproved Use [see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions [see Contraindications (4.1) and Warnings and Precautions (5.4)]
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders [see Warnings and Precautions (5.5)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition [see Warnings and Precautions (5.7)]
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm [see Warnings and Precautions (5.8)]
- Retrolubar Hemorrhages in Patients Treated with BOTOX for Strabismus [see Warnings and Precautions (5.9)]
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity [see Warnings and Precautions (5.10)]
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition [see Warnings and Precautions (5.11)]
- Urinary Tract Infections in Patients with Overactive Bladder [see Warnings and Precautions (5.12)]
- Urinary Retention in Patients Treated for Bladder Dysfunction [see Warnings and Precautions (5.13)]

6.1 Clinical Trials Experience

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

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

In general, adverse reactions occur within the first week following injection of BOTOX and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. 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 11 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 11: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Often than in Placebo-treated Patients Within the First 12 Weeks after Intradermator 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 12.
**Table 14: 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 upper limb spasticity appear in Table 15.

**Table 15: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trials**

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

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

**Lower Limb Spasticity**

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 16. Two hundred thirty-one patients enrolled in a double-blind placebo controlled study (Study 6) received 300 Units to 400 Units of BOTOX, and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

**Table 16: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)**

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

**Cervical Dystonia**

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%). Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinits, dizziness, hypotonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles [see Warnings and Precautions (5.2, 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, pharyngitis, flu syndrome, headache, fever, neck or back pain, prunitus, and anxiety.

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

**Blepharospasm**

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

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

In two cases of VII nerve disorder, reduced blinking from BOTOX injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.
Strabismus
Extracocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%. The incidence of ptosis has been reported to be dependent on the location of the injected muscle. 1% of patients treated with botulinum toxin injection for strabismus 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 orabbler 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; brachial plexopathy; denervation/muscle atrophy; diarrhea; hyperhidrosis; hypoacusis; hypoesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasisform 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 twice during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the maximum recommended human dose of 400 Units on a body weight basis (Units/kg).

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

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 2 times the maximum recommended 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
Bladder Dysfunction
Safety and effectiveness in patients below the age of 18 years have not been established.

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

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

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

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

Blepharospasm and Strabismus
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.
8.5 Geriatric Use
Overall, with the exception of Overactive Bladder (see below), clinical studies of BOTOX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Overactive Bladder
Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 17). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

Table 17: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

<table>
<thead>
<tr>
<th>Age Group during First Placebo-controlled Treatment</th>
<th>&lt;65 Years</th>
<th>65 to 74 Years</th>
<th>≥75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>BOTOX 100 Units (N=344)</td>
<td>Placebo (N=348)</td>
<td>BOTOX 100 Units (N=169)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>73 (21%)</td>
<td>23 (7%)</td>
<td>51 (30%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>21 (6%)</td>
<td>2 (0.6%)</td>
<td>14 (8%)</td>
</tr>
</tbody>
</table>

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

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

Symptoms of overdosage are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see Boxed Warning and Warnings and Precautions (5.2, 5.6)]. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

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

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

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

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan’s products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

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

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

When injected intradermally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating. Following intraderosus injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

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

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX.

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

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

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

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urgency 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 and other secondary variables are shown in Tables 18 and 19, and Figures 5 and 6.
**Table 18: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1**

<table>
<thead>
<tr>
<th>Primary variable</th>
<th>Secondary variable</th>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Frequency of Urinary Incontinence Episodes</td>
<td></td>
<td>BOTOX (N=275)</td>
<td>Placebo (N=272)</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-2.6</td>
<td>-1.0</td>
<td>-1.6</td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-2.8</td>
<td>-1.0</td>
<td>-1.8</td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-2.5</td>
<td>-0.9</td>
<td>-1.6 (-2.1, -1.2)</td>
</tr>
</tbody>
</table>

| Daily Frequency of Micturition Episodes | | BOTOX (N=275) | Placebo (N=272) | Treatment Difference | p-value |
| Mean Baseline | 12.0 | 11.2 | | | |
| Mean Change* at Week 12** | -1.9 | -0.9 | -1.0 (-1.5, -0.6) | <0.001 | |

| Volume Voided per Micturition (mL) | | BOTOX (N=275) | Placebo (N=272) | Treatment Difference | p-value |
| Mean Baseline | 156 | 161 | | | |
| Mean Change* at Week 12** | 38 | 8 | 30 (17, 43) | <0.001 |

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

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

** Primary timepoint

§ Primary variable

© Secondary variable

**Table 19: 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>Primary variable</th>
<th>Secondary variable</th>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Frequency of Urinary Incontinence Episodes</td>
<td></td>
<td>BOTOX (N=275)</td>
<td>Placebo (N=269)</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-2.7</td>
<td>-1.1</td>
<td>-1.6</td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-3.1</td>
<td>-1.3</td>
<td>-1.8</td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-3.0</td>
<td>-1.1</td>
<td>-1.9 (-2.5, -1.4)</td>
</tr>
</tbody>
</table>

| Daily Frequency of Micturition Episodes | | BOTOX (N=275) | Placebo (N=269) | Treatment Difference | p-value |
| Mean Baseline | 12.0 | 11.8 | | | |
| Mean Change* at Week 12** | -2.3 | -0.6 | -1.7 (-2.2, -1.3) | <0.001 | |

| Volume Voided per Micturition (mL) | | BOTOX (N=275) | Placebo (N=269) | Treatment Difference | p-value |
| Mean Baseline | 144 | 153 | | | |
| Mean Change* at Week 12** | 40 | 10 | 31 (20, 41) | <0.001 |

* Least squares (LS) mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. 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

§ Primary variable

© Secondary variable

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

14.2 Detrusor Overactivity associated with a Neurologic Condition

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of 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 20 and 21, and Figures 7 and 8. No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.
Table 20: 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><strong>Weekly Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>134</td>
<td>146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.3</td>
<td>28.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-15.3</td>
<td>-10.0</td>
<td>-5.3</td>
<td>—</td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-19.9</td>
<td>-10.6</td>
<td>-9.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-19.8</td>
<td>-8.8</td>
<td>-11.0</td>
<td>—</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>123</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>253.8</td>
<td>259.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>135.9</td>
<td>12.1</td>
<td>123.9</td>
<td>(89.1, 158.7)</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>41</td>
<td>103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>63.1</td>
<td>57.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-28.1</td>
<td>-3.7</td>
<td>-24.4</td>
<td>—</td>
</tr>
</tbody>
</table>

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

** Primary timepoint
^ Primary endpoint
_ Secondary endpoint

Table 21: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-2

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

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

** Primary timepoint
^ Primary endpoint
_ Secondary endpoint

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

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 22).

Table 22: Week 24 Key Efficacy Variables for Study 1 and Study 2

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

* Significantly different from placebo (p<0.05)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.
Table 23: 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></td>
<td></td>
<td></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></td>
<td></td>
<td></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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adductor Pollicis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Pollicis Longus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> injected only if spasticity is present in this muscle

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

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 24.

Table 24: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>BOTOX (N=64)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint at Week 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flexors muscle tone on the Ashworth Scaleкк</td>
<td>-2.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>finger flexors muscle tone on the Ashworth Scaleкк</td>
<td>-1.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>thumb flexors muscle tone on the Ashworth Scaleкк</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>Median Physician Global Assessment of Response to Treatment†</td>
<td>2.0*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>1</sup> Primary endpoint at Week 6
<sup>2</sup> Secondary endpoints at Week 6
<sup>3</sup> Significantly different from placebo (p≤0.05)
<sup>4</sup> BOTOX injected into both the flexor carpi radialis and ulnaris muscles
<sup>5</sup> BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
<sup>6</sup> BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 patients (BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)) with upper limb spasticity (expanded Ashworth score of at least 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 25).

Table 25: Study Medication Dose and Injection Sites in Study 2 and Study 3

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX low dose (90 Units)</td>
</tr>
<tr>
<td>Wrist</td>
<td></td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>10 Units</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>15 Units</td>
</tr>
<tr>
<td>Finger</td>
<td></td>
</tr>
<tr>
<td>Flexor Digitorum Profundus</td>
<td>7.5</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>7.5</td>
</tr>
<tr>
<td>Elbow</td>
<td></td>
</tr>
<tr>
<td>Biceps Brachii</td>
<td>50 Units</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 26.
Study 5 was 12 weeks.

**Table 28: Study Medication Dose and Injection Sites in Studies 4 and 5**

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(Units)</td>
<td>(mL)</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(N=21)</td>
</tr>
<tr>
<td></td>
<td>mid dose</td>
<td>(N=23)</td>
</tr>
<tr>
<td></td>
<td>high dose</td>
<td>(N=21)</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(N=26)</td>
</tr>
<tr>
<td></td>
<td>mid dose</td>
<td>(N=21)</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 29. The MAS uses a similar scoring system as the Ashworth Scale.

**Table 29: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4**

<table>
<thead>
<tr>
<th></th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N=66)</td>
<td>(N=57)</td>
</tr>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified 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>

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale (−5 worst possible function to +5 best possible function) are presented in Table 30.

**Table 30: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5**

<table>
<thead>
<tr>
<th></th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(Units)</td>
<td>(mL)</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(N=14)</td>
</tr>
<tr>
<td></td>
<td>mid dose</td>
<td>(N=9)</td>
</tr>
<tr>
<td></td>
<td>high dose</td>
<td>(N=43)</td>
</tr>
<tr>
<td></td>
<td>low dose</td>
<td>(N=23)</td>
</tr>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale††</td>
<td>-1.0</td>
<td>-0.5*</td>
</tr>
<tr>
<td>Median Change from Baseline in Clinical Global Impression Score by Physician††</td>
<td>1.0</td>
<td>2.0*</td>
</tr>
</tbody>
</table>

**Lower Limb Spasticity**

The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 31) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.
The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4 = very marked worsening to +4 = very marked improvement.

Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 32).

### Table 32: Co-Primary Efficacy Endpoints Results in Study 6 (Intent-to-treat Population)

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>BOTOX (Units)</th>
<th>Placebo (N=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandatory Ankle Muscles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrocnemius (medial head)</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Gastrocnemius (lateral head)</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Soleus</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td>75</td>
<td>3</td>
</tr>
<tr>
<td>Optional Muscles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor Hallucis Longus</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Flexor Digitorum Longus</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Flexor Digitorum Brevis</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Extensor Hallucis</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Rectus Femoris</td>
<td>100</td>
<td>4</td>
</tr>
</tbody>
</table>

* Significantly different from placebo (p<0.05)

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

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

### Table 33: Study Medication Dose and Injection Sites in Study 6

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Treatment Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor Hallucis Longus</td>
<td>300 to 400 Units (N=233)</td>
</tr>
<tr>
<td>Flexor Digitorum Brevis</td>
<td>300 to 400 Units (N=233)</td>
</tr>
<tr>
<td>Extensor Hallucis</td>
<td>300 to 400 Units (N=233)</td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td>300 to 400 Units (N=233)</td>
</tr>
<tr>
<td>Rectus Femoris</td>
<td>300 to 400 Units (N=233)</td>
</tr>
</tbody>
</table>

**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 enrollment period where they received their previously employed dose of BOTOX. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician’s evaluation of the patient’s 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 33.

### Table 33: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=82)</th>
<th>BOTOX (N=88)</th>
<th>95% CI on Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CDSS</td>
<td>9.3</td>
<td>9.2</td>
<td>(-2.3, 0.3)</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>Change in 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.
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 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”. A total of 322 patients were randomized in a 1:1:1 ratio to treatment with BOTOX, placebo, or no treatment. 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.

In the study, the percentages of responders were 91% (219/242) in the BOTOX group and 36% (29/81) 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 35: 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 (%)</td>
<td>55% (57)</td>
<td>49% (54)</td>
<td>6% (6)</td>
<td>49.3% (38.8, 59.7)</td>
<td>43% (33.2, 53.8)</td>
</tr>
<tr>
<td>&gt;50% decrease in axillary sweat production % (n)</td>
<td>81% (84)</td>
<td>86% (94)</td>
<td>41% (44)</td>
<td>40% (28.1, 52.0)</td>
<td>45% (33.3, 56.1)</td>
</tr>
</tbody>
</table>

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

### Table 34: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

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

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

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

14.7 Blepharospasm

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

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

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

14.8 Strabismus

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

### HOW SUPPLIED/STORAGE AND HANDLING

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

Vials of BOTOX have a holographic film on the vial label that contains the name “Allergan” within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) If you do not see the lines of rainbow color or the name “Allergan”, do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

**Storage**

Unopen 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.
2. Spread of toxin effects.

Problems after injection of BOTOX or BOTOX Cosmetic

Swallowing, Speaking, or Breathing Difficulties, or Other Unusual Symptoms

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens. (See Boxed Warning and Warnings and Precautions (5.2, 5.6).

Ability to Operate Machinery or Vehicles

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

17 PATIENT COUNSELING INFORMATION

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

MEDICATION GUIDE

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

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

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

- Problems breathing or swallowing
- Spread of toxin effects

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

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
- Drooping eyelids
- Double vision
- Blurred vision
- 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 due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- To prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- To treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- To treat increased muscle stiffness in ankle and toe muscles in adults with lower limb spasticity.
- To treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- To treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

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

BOTOX Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults for a short period of time (temporary).

BOTOX Cosmetic is a prescription medicine that is injected into the area around the side of the eyes to improve the look of crow’s feet lines in adults for a short period of time (temporary).

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

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

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm
**BOTOX Cosmetic** is not recommended for use in children younger than 13 years of age.

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

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

**Who should not take BOTOX or BOTOX Cosmetic?**

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

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

**What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?**

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

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig’s disease], myasthenia gravis or Lambert-Eaton syndrome). See “What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?”
- have allergies to any botulinum toxin product.
- had any side effect from any botulinum toxin product in the past.
- have or have had a breathing problem, such as asthma or emphysema.
- have or have had swallowing problems.
- have plans to have surgery.
- had surgery on your face.
- have weakness of your forehead muscles, such as trouble raising your eyebrows.
- have drooping eyelids.
- have any other change in the way your face normally looks.
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence.
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and 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?**

**Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.**

**BOTOX** is injected into your affected muscles, skin, or bladder. **BOTOX Cosmetic** is injected into your affected muscles.

**What should I avoid while taking BOTOX or BOTOX Cosmetic?**

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

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

**BOTOX** and **BOTOX Cosmetic** can cause serious side effects. See “What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?”
Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- 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