CLINICAL INTRODUCTION TO BOTOX®

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**

The important role you play within your provider’s practice involves one or more key aspects of the patient’s journey through their treatment with BOTOX® (onabotulinumtoxinA). This module is intended to provide a brief overview of BOTOX® to help you understand what it is and how it is used to help manage some of the patients your provider(s) treats. While provider(s) are responsible for all of the clinical decisions around BOTOX® treatment, the information in this module may help you to gain an even greater appreciation for the ways in which you can best support BOTOX® patients with their ongoing treatment.

**Overview**

BOTOX® is an injectable treatment that is given by an appropriate provider to patients with one or more of a number of approved medical conditions that will be detailed in the following section. As for all prescription medications, the Federal Drug Administration (FDA) has approved each of these conditions for BOTOX® treatment based on the clinical trials that have shown the treatment to be safe and effective at specific doses, and with treatments recommended to be repeated at certain intervals of time. Your provider(s) will determine the specific patients to be treated and the dose and frequency of injections based on the ongoing evaluation of the patient.

**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.
Approved Medical Conditions

One or more of the following medical conditions may be ones that your providers treat in their practice, and each of these has been approved by the FDA for the treatment with BOTOX® (onabotulinumtoxinA). Brief explanations of the most common conditions your providers may be treating are outlined in the following sections. You may also consider performing your own research to learn more about the patient types your provider(s) treats most often.

Notes

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.

Please see additional Important Safety Information about BOTOX® on following pages.
How is BOTOX® (onabotulinumtoxinA) treatment given?

BOTOX® comes in a vial that needs to be kept at a cool temperature until your provider is ready to mix it with saline before the patient is due to be injected.

Depending on the medical condition being treated, BOTOX® is injected into specific muscles or areas of the body according to the FDA prescribing information and the provider’s clinical judgment. The dose required for the treatment may involve more than one vial being used per patient.

Patients being injected for the first time may be nervous about what to expect. Everyone in the office can play a role in making the visit as easy as possible for the patient so that he or she may have the best experience in the practice as possible and help patients become committed to following the ongoing treatment plan your provider recommends for them.

Repeat treatments

Patients that receive BOTOX® treatment will usually need to continue to receive subsequent injections. BOTOX® is a temporary treatment which varies per indication, so for continued treatment benefit, the patient will need to continue to receive BOTOX® treatments as recommended by the provider. Depending on the condition being treated, the treatment intervals will vary. Repeat BOTOX® treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks or 3 months after the previous injection.

See the following information for further detail around conditions your provider may treat with BOTOX®.

Notes

IMPORTANT SAFETY INFORMATION (continued)

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.

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.

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.
Blepharospasm

Patients suffering with Blepharospasm are troubled by spasms of the muscles around the eye, resulting in uncontrolled blinking, narrowing, and even closing of the eyelid. At this time, it is unknown what exactly causes the eye muscles to contract in this manner. Your provider will administer BOTOX® (onabotulinumtoxinA) to the patient by injecting directly into the muscles. Following injection, the patient may begin seeing an improvement in their symptoms within the first 3 days, with maximum results 1 to 2 weeks after their injection. Repeat treatments may be administered (per physician’s clinical decision) once the effect of the previous injection has worn off, but no sooner than every 3 months.

Cervical Dystonia

Patients with Cervical Dystonia typically suffer with discomfort in their head and neck resulting from muscle spasms that can force abnormal and involuntary movements. This condition can be very challenging and painful. Your provider will inject BOTOX® directly into the patient’s affected muscles. Sometimes the provider will use a special guidance machine such as an electromyograph (EMG) to make sure the injections are placed as accurately as possible. It usually takes longer than 1 treatment cycle to see the full benefit from BOTOX®, and repeat treatments may be administered (per physician’s clinical decision) after the effect of the previous injection has worn off, but no sooner than every 3 months. With Cervical Dystonia, the wide variability in patients’ presentation, condition, and/or response to treatment or muscle mass often results in this described scenario where a provider will need to spend time tailoring the dose and muscle selection over more than one treatment cycle for a given patient.

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.
Chronic Migraine

Patients with Chronic Migraine typically suffer with headaches and migraines on more days in the month than days they are headache free. They can suffer from nausea and/or vomiting, blurred vision and can experience sensitivity to light and loud noises. Your provider may consider such patients for treatment with BOTOX® (onabotulinumtoxinA) if they experience 15 or more days each month with headache, lasting 4 hours or longer each day. BOTOX® is designed to prevent these headaches before they start. Your provider will inject BOTOX® into certain head and neck muscle areas. It usually takes longer than 1 treatment cycle (12 weeks) to see a benefit with BOTOX® with primary efficacy endpoint at 24 weeks. Repeat treatments are recommended every 12 weeks (per physician’s clinical decision).

Upper Limb Spasticity

Patients who suffer from Upper Limb Spasticity typically have stiffness in their elbow, wrist, fingers, or thumb muscles. This tightness and contraction of the muscles may be caused by one or more conditions such as Stroke, Traumatic brain injury (TBI), Multiple sclerosis (MS), Spinal cord injury (SCI), Adult cerebral palsy which can damage the brain or the spinal cord. Upper limb spasticity patients may have one or more of the following: a wrist that is bent downward, an elbow that is flexed stiffly against their chest, a fist that is clenched, and/or a thumb that is curled into their palm.

Your provider will inject BOTOX® into the affected muscles to help reduce stiffness and tightness and will typically use EMG or other guidance to make sure the injections are placed as accurately as possible.

Repeat treatments may be administered (per physician’s clinical decision) after the effect of the previous injection has worn off, but no sooner than 12 weeks after the previous injection. Remember, it may take longer than 1 treatment cycle to see a benefit with BOTOX®. That is why it is important for the patient to come back regularly as directed by your provider.

Are there any additional indications that you would like to discuss with your provider that were not listed?

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.
Allergan Support Team

Your BOTOX® (onabotulinumtoxinA) patients and practice are supported by a team of Allergan resources, both clinical and operational.

- Your Allergan sales representative (Neuroscience Sales Specialist or Health Systems Manager) provides clinical support for all appropriate BOTOX® patients for therapeutic indications such as Chronic Migraine, Upper Limb Spasticity, which is stiffness of the elbow, wrist, fingers, and thumb and Cervical Dystonia. Patient brochures and other resources are available on request.

- The Allergan Neuroscience Business Practice Specialist (NBPS) provides operational support to help streamline office processes (including those involved in the reimbursement steps) associated with treating BOTOX® patients.

Your local Allergan team works together with your practice to support all of the needs of your BOTOX® patients. Each support team member delivers specific training and resources to help simplify the path to BOTOX® for appropriate patients your provider(s) choose to treat in your practice.

Notes

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).

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.

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.

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%).

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

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.

ADVERSE REACTIONS

The following adverse reactions to BOTOX® (onabotulinumtoxinA) 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 Strabismus (see Warnings and Precautions); and Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity (see Warnings and Precautions).

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%), myalgia (3%), facial paresis (2%), hypertension (2%), and muscle spasms (2%).

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.

Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® 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 aminoglycosides 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.
Clinical Introduction to BOTOX® (onabotulinumtoxinA)

Module Quiz

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

1. BOTOX® is an injectable treatment that is given by a provider to appropriate patients with one or more of a number of approved medical conditions.

2. BOTOX® comes in a vial that needs to be kept at a very warm temperature.

3. Patients may receive more than one BOTOX® treatment (per physician’s clinical decision).

4. Patients with Chronic Migraine typically suffer with headaches and migraines on more days in the month than days they are headache free.

5. It may take longer than 1 treatment cycle to see a benefit with BOTOX®.
Clinical Introduction to BOTOX® (onabotulinumtoxinA)

Module Quiz: Answer Key

1. True

2. False

3. True

4. True

5. True
BOTOX® Patient Navigator Program

Certificate of Completion

This certificate is to be presented to

For the successful completion of the CLINICAL INTRODUCTION TO BOTOX® module

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

Completion Date
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)

Dosage and Administration (2.1, 2.5) 01/2016

- Indications and Usage, Spasticity (1.3) 01/2016
- Dosage and Administration (2.1, 2.5) 01/2016
- Warnings and Precautions (5.3, 5.10) 01/2016

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

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

Initial U.S. Approval: 1989

**WARNING: DISTANT SPREAD OF TOXIN EFFECT**

See full prescribing information for complete boxed warning.

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

**RECENT MAJOR CHANGES**

- Indications and Usage, Spasticity (1.3)
- Dosage and Administration (2.1, 2.5)
- Warnings and Precautions (5.3, 5.10)

**INDICATIONS AND USAGE**

BOTOX is not interchangeable with other preparations of botulinum toxin products (5.11)

- 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)
- Urinary tract infections 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
1.5 Primary Axillary Hyperhidrosis
BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

1.6 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.

2. DOSEAGE AND ADMINISTRATION
2.1 Instructions for Safe Use
The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX are measured by a specific bioassay method. Units of biological activity are expressed in terms of the number of botulinum neurotoxin type A units contained in each dose. The potency of BOTOX is estimated using a mouse bioassay method. The specific potency of BOTOX is determined by comparing the number of units in each dose of BOTOX to the number of units in a standard of known potency. The standard used for the determination of potency is the 1.0 U/mL standard.

2.2 Preparation and Dilution Technique

2.3 Bladder Dysfunction
BOTOX is indicated for the treatment of spasticity in pediatric patients under age 18 years.

2.4 Chronic Migraine
BOTOX is indicated for the treatment of chronic migraine associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

2.5 Spasticity

2.6 Cervical Dystonia
BOTOX is indicated for the treatment of cervical dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

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

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

2.9 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.

3. DOSAGE FORMS AND STRENGTHS

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

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

6. ADVERSE REACTIONS

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

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Nursing Mothers
8.3 Pediatric Use
8.4 Geriatric Use

9. OVERDOSAGE
9.1 General

10. CLINICAL STUDIES
10.1 Overview
10.2 Detrusor Overactivity associated with a Neurologic Condition

11. DESCRIPTION
11.1 Mechanism of Action
11.2 Pharmacokinetics

12. CLINICAL PHARMACOLOGY

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology

14. CLINICAL STUDIES
14.1 Detrusor Overactivity associated with a Neurologic Condition
14.2 Detrusor Overactivity associated with a Neurologic Condition

15. PATIENT COUNSELING INFORMATION

16. HOW SUPPLIED/STORAGE AND HANDLING

17. FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT
Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, paresis, 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. [See Warnings and Precautions (5.2)]
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. 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 24 hours after reconstitution. During this time period, reconstituted BOTOX should be stored in a refrigerator (2°C to 8°C).

2.3 Bladder Dysfunction

General

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics, except aminoglycosides, 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 exceed.

200 Unit Vial of BOTOX

- Reconstitute a 100 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 1 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.
Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, placebo-controlled clinical studies was 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.4 Chronic Migraine

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL (see Table 1). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per 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</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 2) at a given treatment session.

Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose (Number of Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps brachii</td>
<td>100 Units-200 Units divided in 4 sites</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>12.5 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>12.5 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>30 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>30 Units-50 Units in 1 site</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>20 Units in 1 site</td>
</tr>
<tr>
<td>Flexor pollicis longus</td>
<td>20 Units in 1 site</td>
</tr>
</tbody>
</table>

Figure 2: Injection Sites for Upper Limb Spasticity

Lower Limb Spasticity

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

Table 4: BOTOX Dosing by Muscle for Lower Limb Spasticity

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose (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 digitorum longus</td>
<td>50 Units divided in 2 sites</td>
</tr>
</tbody>
</table>

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 (14.5)].

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

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

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

2.7 Primary Auxiliary Hyperhidrosis
The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor’s Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Table 1). Using a sterile 30 gauge needle, 50 Units of BOTOX (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart. Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

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

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 4.

Figure 4: Injection Pattern for Primary Auxiliary Hyperhidrosis

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

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

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

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

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

2.9 Strabismus
BOTOX is intended for injection into 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 motor fusion to stabilize the alignment.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS
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 asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms may 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, dysarthria, 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 Neurologic Condition

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely in a double-blind, placebo-controlled, parallel group study in 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>3%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Week 12</td>
<td>10%</td>
<td>5%</td>
<td>2%</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 Forcéd 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>≥15%</td>
</tr>
<tr>
<td>Week 2</td>
<td>0/12 (0%)</td>
<td>1/11 (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>0/6 (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 reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

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

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

5.13 Urinary Retention in Patients Treated for Bladder Dysfunction
Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

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

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

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></td>
<td>Min, Max: 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)]
- **Retrolubular 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 12: Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to History of Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>BOTOX 100 Units (N=81)</td>
<td>25 (31%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>8 (3%)</td>
<td>64 (24%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>45 (17%)</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>24 (4%)</td>
<td>11 (2%)</td>
</tr>
</tbody>
</table>

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively.

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 200 Units (N=262)</th>
<th>Placebo (N=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>64 (24%)</td>
<td>47 (17%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>45 (17%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>10 (4%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

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

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

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

**Chronic Migraine**

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

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 14.

* 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.
Those reported in patients treated for upper limb spasticity with 360 Units of BOTOX. Adverse reactions observed in patients treated with 400 Units of BOTOX were similar to approximately one year for treatment of upper limb spasticity. The type and frequency of 44 Twenty-two adult patients, enrolled in double-blind placebo controlled studies, 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.

### Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult upper 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>
<thead>
<tr>
<th>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)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reactions</strong></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Infections and infestations</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
</tr>
<tr>
<td>Injection site pain</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, rhinitis, dizziness, hypotonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dysphagia 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 dysphoria [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 dysphoria in patients who have been treated for cervical dystonia.

### Primary Axillary Hyperhidrosis

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

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

### Blepharospasm

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

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

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

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**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>6 (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>49 (8%)</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 300 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.
Strabismus
Extraciliary muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%. The incidence of ptosis has been reported to be dependent on the location of the injected muscles.1% after horizontal rectus injections, 16% after vertical rectus injections and 38% after superior rectus injections.

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

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

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

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), no patients among 406 migraine patients, no patients among 615 oculomotor/oculomotor 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 measured antibody levels (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; demerivation/muscle atrophy; diarrhea; hyperhidrosis; hypoacusis; hypoesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

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

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

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

7 DRUG INTERACTIONS
7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission
Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

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

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
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 two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the 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.

Ayillary 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 dosage 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 |
|----------------------------------|----------------------------------|----------------------------------|
|                                  | <65 Years                        | 65 to 74 Years                   | ≥75 Years                        |
| Adverse Reactions                | BOTOX 100 Units (N=344)          | Placebo (N=348)                  | BOTOX 100 Units (N=169)          | Placebo (N=151)                  | BOTOX 100 Units (N=94)           | Placebo (N=86)                  |
| Urinary tract infection          | 73 (21%)                        | 23 (7%)                         | 51 (30%)                        | 20 (13%)                        | 36 (38%)                        | 8 (9%)                          |
|                                 | (N=169)                          | (N=151)                         | (N=94)                          | (N=86)                          |
| Urinary retention                | 21 (6%)                         | 2 (0.6%)                        | 14 (8%)                         | 0 (0%)                          | 8 (9%)                          | 1 (1%)                          |

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

10 OVERDOSAGE
Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see Boxed Warning and Warnings and Precautions (5.2, 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 found 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, intradermal injection. 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 intradernally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating. Following intradermor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

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

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

Mutagenesis
BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic 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 urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 18 and 19, and Figures 5 and 6.
**Primary timepoint**

**Least squares (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. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.**

**Primary variable**

**Secondary variable**

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

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units (N=278)</th>
<th>Placebo (N=272)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-2.6</td>
<td>-1.0</td>
<td>-1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-2.8</td>
<td>-1.0</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-2.5</td>
<td>-0.9</td>
<td>-1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(± SE)</td>
<td>(-2.1, -1.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volume Voided per Micturition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>156</td>
<td>161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change1 at Week 12**</td>
<td>38</td>
<td>8</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(± SE)</td>
<td>(17, 43)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

** Primary timepoint

a Primary variable

b Secondary variable

### Table 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></th>
<th>BOTOX 100 Units (N=275)</th>
<th>Placebo (N=269)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-2.7</td>
<td>-1.1</td>
<td>-1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-3.1</td>
<td>-1.3</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-3.0</td>
<td>-1.1</td>
<td>-1.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(± SE)</td>
<td>(-2.5, -1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Daily Frequency of Micturition Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>12.0</td>
<td>11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change1 at Week 12**</td>
<td>-2.3</td>
<td>-0.6</td>
<td>-1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(± SE)</td>
<td>(-2.2, -1.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Volume Voided per Micturition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>144</td>
<td>153</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change1 at Week 12**</td>
<td>40</td>
<td>10</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(± SE)</td>
<td>(20, 41)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.

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

** Primary timepoint

a Primary variable

b Secondary variable

### Figure 5: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-1

- Treatment
  - Placebo (n=272)
  - BOTOX® 300 U (n=278)

- p-value
  - <0.001

### Figure 6: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-2

- Treatment
  - Placebo (n=272)
  - BOTOX® 100 U (n=278)

- p-value
  - <0.001

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 6. 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>Treatment</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>134</td>
<td>146</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.3</td>
<td>28.3</td>
</tr>
<tr>
<td>Mean Change at Week 2</td>
<td>-15.3</td>
<td>-10.0</td>
</tr>
<tr>
<td>Mean Change at Week 6**</td>
<td>-19.9</td>
<td>-10.6</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-19.8</td>
<td>-8.8</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> (mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>123</td>
<td>129</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>253.8</td>
<td>259.1</td>
</tr>
<tr>
<td>Mean Change at Week 6**</td>
<td>135.9</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> (cmH₂O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>41</td>
<td>103</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>63.1</td>
<td>57.4</td>
</tr>
<tr>
<td>Mean Change at Week 6**</td>
<td>-28.1</td>
<td>-3.7</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>Treatment</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.7</td>
<td>36.8</td>
</tr>
<tr>
<td>Mean Change at Week 2</td>
<td>-18.0</td>
<td>-7.9</td>
</tr>
<tr>
<td>Mean Change at Week 6**</td>
<td>-19.6</td>
<td>-10.8</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-19.6</td>
<td>-10.7</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> (mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>239.6</td>
<td>253.8</td>
</tr>
<tr>
<td>Mean Change at Week 6**</td>
<td>150.8</td>
<td>2.8</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> (cmH₂O)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>68</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>65.6</td>
<td>43.7</td>
</tr>
<tr>
<td>Mean Change at Week 6**</td>
<td>-28.7</td>
<td>2.1</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 (N=341)</th>
<th>Study 2 (N=347)</th>
<th>Placebo (N=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in frequency of headache days</td>
<td>-7.8*</td>
<td>-9.2*</td>
<td>-6.9</td>
</tr>
<tr>
<td>Change from baseline in total cumulative hours of headache on headache days</td>
<td>-107*</td>
<td>-70</td>
<td>-134*</td>
</tr>
</tbody>
</table>

* Significantly different from placebo (p<0.05)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.
Figure 9: Mean Change from Baseline in Number of Headache Days for Study 1

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

14.4 Spasticity

Upper Limb Spasticity

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

Study 1 included 126 patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus muscles (see Table 23). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

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><strong>Wrist</strong></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><strong>Finger</strong></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><strong>Thumb</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>0.4</td>
<td>20</td>
<td>1</td>
</tr>
</tbody>
</table>

* injected only if spasticity is present in this muscle

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

* Primary endpoint at Week 6
† Secondary endpoints at Week 6
†† Significantly different from placebo (p≤0.05)
††† BOTOX injected into both the flexor carpi radialis and ulnaris muscles
†††† BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
‡ 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>BOTOX low dose (90 Units)</th>
<th>BOTOX mid dose (180 Units)</th>
<th>BOTOX high dose (360 Units)</th>
<th>Volume (mL) per site</th>
<th>Injection Sites (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wrist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>10 Units</td>
<td>20 Units</td>
<td>40 Units</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>15 Units</td>
<td>30 Units</td>
<td>60 Units</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Finger</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor Digitorum Profundus</td>
<td>7.5 Units</td>
<td>15 Units</td>
<td>30 Units</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>7.5 Units</td>
<td>15 Units</td>
<td>30 Units</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Elbow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps Brachii</td>
<td>50 Units</td>
<td>100 Units</td>
<td>200 Units</td>
<td>0.5</td>
<td>4</td>
</tr>
</tbody>
</table>

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

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 26.
Study 5 was 12 weeks.

Study 4 included 170 patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 5, patients received BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)).

Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 patients (BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 27.

Table 27: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

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

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 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>Muscles Injected</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX (N=66)</td>
</tr>
<tr>
<td>Primary endpoint at Week 6</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Secondary endpoints at Week 6</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Dose of BOTOX injected into biceps brachii muscle</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
</tbody>
</table>

Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with 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 6 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.

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX (N=66)</td>
</tr>
<tr>
<td>Primary endpoint at Week 6</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Secondary endpoints at Week 6</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles</td>
<td>* Significantly different from placebo (p≤0.05)</td>
</tr>
<tr>
<td>Dose of BOTOX injected into biceps brachii muscle</td>
<td>* Significantly different from placebo (p≤0.05)</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 6 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected into the adductor pollicis and flexor pollicis longus muscles.
14.5 Cervical Dystonia

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

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allot a point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician’s evaluation of the patients’ status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 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]α</td>
</tr>
<tr>
<td>Change in CDSS at Week 6</td>
<td>-0.3</td>
<td>-1.3</td>
<td>(-2.3, -0.3)α</td>
</tr>
<tr>
<td>% Patients with Any Improvement on Physician Global Assessment</td>
<td>31%</td>
<td>51%</td>
<td>(5%, 34%)β</td>
</tr>
<tr>
<td>Pain Intensity Baseline</td>
<td>1.8</td>
<td>1.8</td>
<td>0.0</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)β</td>
</tr>
<tr>
<td>Pain Frequency Baseline</td>
<td>1.9</td>
<td>1.8</td>
<td>0.0</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)β</td>
</tr>
</tbody>
</table>

α Confidence intervals are constructed from the analysis of covariance table with analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
β 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.
γ Confidence intervals are based on the t-distribution.
Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 34. The total dose and muscles selected were tailored to meet individual patient needs.

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

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

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

14.6 Primary Axillary Hyperhidrosis

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = “underarm sweating is never noticeable and never interferes with my daily activities”; 2 = “underarm sweating is noticeable and infrequently 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 in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg of sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

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

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

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group (p<0.001), but was not significantly different between the two BOTOX doses (see Table 35).

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

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

Table 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 (n)*</td>
<td>55% (57)</td>
<td>49% (54)</td>
<td>6% (6)</td>
<td>49.3% (38.8, 59.7)</td>
<td>43% (33.2, 53.8)</td>
</tr>
<tr>
<td>&gt;50% decrease in axillary sweat production % (n)</td>
<td>81% (84)</td>
<td>86% (94)</td>
<td>41% (44)</td>
<td>40% (28.1, 52.0)</td>
<td>45% (33.3, 56.1)</td>
</tr>
</tbody>
</table>

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

14.7 Blepharospasm

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

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

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

14.8 Strabismus

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

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX 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

Unopened vials of BOTOX should be stored in a refrigerator (2° to 8°C) for up to 36 months. Do not use after the expiration date on the vial. Administer BOTOX within 24 hours of reconstitution; during this period reconstituted BOTOX should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX should be clear, colorless, and free of particulate matter.
1. Spread of toxin effects. In some cases, the effect of botulinum
toxin may affect areas of the body away from the injection site
and cause symptoms of a serious condition called botulism. The
symptoms of botulism include:
- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

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

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

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

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles
and used:
- to treat overactive bladder symptoms such as a strong need
to urinate with leaking or wetting accidents (urge urinary
incontinence), a strong need to urinate right away (urgency),
and urinating often (frequency) in adults when another type of
medicine (anticholinergic) does not work well enough or cannot
be taken.
- to treat leakage of urine (incontinence) in adults with overactive
bladder 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 18 years of age.

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

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

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

Tell your doctor if you:

- have or have had 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).

Your doctor will tell you how often you will receive your dose of BOTOX Cosmetic. Your doctor may change your dose of BOTOX or BOTOX Cosmetic, until you and your doctor find the best dose for you.

**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