Developing a Patient Welcome Letter
BOTOX® (onabotulinumtoxinA) for appropriate patients

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

Detrusor Overactivity Associated With a Neurologic Condition
BOTOX® is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

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, wrist, finger, and thumb flexors (biceps, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum sublimis, 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 or 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.

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.

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 Important Safety Information about BOTOX® on following pages.
Overview

This guide is designed to assist in providing considerations for the development of a patient welcome letter that may help provide relevant practice information and set appropriate patient expectations around BOTOX® treatment.

It is important to recognize that every practice is unique, and the utilization of this guide is intended only to provide considerations that should be tailored to individual practice needs. You should follow your specific practice policies and guidelines that govern the development of patient materials.

Creating a Welcome Letter for Your BOTOX® (onabotulinumtoxinA) Patients

Providing information about your BOTOX® treatment program is an essential aspect of the patient journey. It allows you to welcome a new patient into your practice, and can be a first step in establishing relationships between the patient and the treatment team. A welcome letter allows you to provide relevant information about treatment with BOTOX®, such as clinical and financial education, details about treatment expectations, and the patient’s role in his or her journey through your BOTOX® program. By providing this information, it can help set appropriate expectations that may help to enhance the patient journey and experience in your program.

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.

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 (UTI). 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).

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

Creating a patient welcome letter should be viewed as an opportunity to connect with your patient and convey important information about your BOTOX® (onabotulinumtoxinA) treatment program that will be the foundation for a positive patient experience. Here are a few considerations for getting started:

1. Meet as a treatment team to identify information you want to include in the welcome letter.
2. Agree upon distribution method (email, print, website, patient portal, etc.).
3. Identify a person within the team to be a leader for development of the letter.
4. Use practice/program-specific branding or letterhead.
5. Ask for feedback from patients to enable you to update and modify the letter, ensuring you are setting appropriate patient expectations.

Considerations for What to Include

While all practices are unique, there is some basic information you may consider including in your patient welcome letter. Your practice’s experience in treating BOTOX® patients will likely help you identify specific areas you would like to emphasize in this letter in order to enhance patients’ understanding of the treatment plan. The following sample topics and language may also help guide you as you develop a welcome letter for your BOTOX® patients. Topics might include:

- Introduction
- Your Treatment Team
- Our Program
- Typical Treatment Plan
- How We Work With Your Health Plan
- Your Financial Responsibilities
- How You Can Help
- Contacting Us
- Frequently Asked Questions

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.

Please see additional Important Safety Information about BOTOX® on following pages.
Sample BOTOX® (onabotulinumtoxinA)
Patient Welcome Letter

WELCOME TO THE [INSERT PRACTICE NAME] BOTOX® (onabotulinumtoxinA) TREATMENT PROGRAM

We are pleased to welcome you to our BOTOX® treatment program. Your physician is recommending treatment with BOTOX® for your specific medical condition. This letter is designed to provide you with important information regarding the treatment plan that you and your physician have discussed. Our goal is to make sure you fully understand how this treatment may benefit your medical condition, and to help you understand how you can play an active role in your treatment decisions and ongoing care.

Here, your practice may consider inserting more specific information related to BOTOX® treatment for appropriate patients including risks/benefits, additional patient education, website resources, etc.

Your Treatment Team

Consider providing credentialing information about each team member who will be involved in the BOTOX® treatment program:

- Physician/provider’s credentials, relevant experience, etc.
- Advanced practice provider(s)’ (NP/PA) specific roles, relevant experience, etc.
- BOTOX® Patient Navigator/Insurance Specialist, or other key personnel and their specific roles, relevant experience, etc.

Our Program

Consider providing an overview of your practice model including use of NP/PAs, your practice’s team-based approached to care, shared patient care, etc.

Typical Treatment Plan

Here, consider providing an outline of different appointment types, who may be involved, and what is expected to happen (e.g., injections only on treatment days with prescription refills and other concerns managed during separate appointments, keeping appropriate documentation of your symptoms as requested by your provider, in between appointments to help us fully evaluate benefits of treatment):

- New consultation: You may choose to include appointment length, who the patient will see during their appointment, what to bring, etc.

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

Spread of Toxin Effect

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for chronic migraine at the labeled doses have been reported.

Please see additional Important Safety Information about BOTOX® on following pages.
Typical Treatment Plan (continued)

- **First injection**: Perhaps include appointment length, who the patient will see during the appointment, what to wear, what to bring, treatment expectations, post-treatment instructions (work, driving, etc.).

- **Follow-up appointments**: Consider including the importance of these appointments for the patient, for example: Committing to the BOTOX® (onabotulinumtoxinA) treatment sessions your provider has recommended is important in order to help determine if this treatment is working for you. Re-treatment will be determined by your provider and may vary by use based upon clinical trials.

**Chronic Migraine:**
It may take up to a few weeks to see a response from BOTOX® treatment. For example, in clinical trials, Chronic Migraine patients treated with BOTOX® showed a response at their 4-week evaluation and after 2 treatments (each given at 12 week intervals), BOTOX® was proven to significantly reduce the number of headache days each month vs placebo.¹

**Adult Spasticity:**
Patients can get treated again after the effect of the previous injection has worn off, but no sooner than 3 months from the previous injection. It may take longer than 1 treatment cycle to see a benefit with BOTOX®. That is why it is important to come back approximately every 3 months.

**Overactive Bladder:**
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 169 days [-24 weeks], but no sooner than 12 weeks from the prior bladder injection¹).

- **Additional injections**: It could be helpful to mention frequency, a reminder that full benefit of the treatment may not be experienced after the first injection, and the importance of adhering to the follow-up appointments recommended by the provider.

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**IMPORTANT SAFETY INFORMATION** (continued)

**WARNINGS AND PRECAUTIONS** (continued)

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

Please see additional Important Safety Information about BOTOX® on following pages.
Sample BOTOX® (onabotulinumtoxinA) Patient Welcome Letter (continued)

How We Work With Your Health Plan

Consider providing an overview of the treatment approval process, for example:

Prior to treating you with BOTOX®, we must first receive approval from your insurance company. We will submit information to your insurance company that was gathered during your visit with the provider. As part of that process, we confirm plan coverage and benefits including co-pays, co-insurance, and deductible amounts. This can take 2 to 4 weeks depending on your health plan. Some plans require additional information from the physician and may require separate approvals for the injection procedure and the drug.

In some cases, we will need to obtain the BOTOX® medication through a specialty pharmacy. If this is required, you will be contacted directly by the specialty pharmacy to provide permission for the drug to be delivered to the practice for your treatment, and for the pharmacy to collect any co-payment that is required for the drug.

• Consider providing information about scheduling per the practice policy, whether before or after treatment approval is received (e.g., pre-scheduling and honoring follow-up appointments, giving adequate notice if/when you need to re-schedule an appointment, etc.).

• Provide information about approvals for re-treatment, for example: Depending on the requirements of your insurance company, we will need to obtain approval for ongoing treatment at certain intervals. In order to assist with this, it will be important for you to provide information about the treatment effectiveness to the provider at each appointment. This may include regular completion of your symptom diary.

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.

Increased Risk of Clinically Significant Effects With Pre-Existing Neuromuscular Disorders

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

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

For this section, an overview of the practice’s policies may be helpful, for example:

Prior to your first BOTOX® (onabotulinumtoxinA) treatment, we will let you know the amount you may be responsible to pay. Payment options include: (insert specifics as per the practice policy regarding collection of co-pays/deductibles, outstanding balances, etc.).

For certain types of insurance, assistance may be available to help you with your co-pay amounts for BOTOX®. We can provide you with information about the BOTOX® Savings Card and help you register for this program.

How You Can Help

Consider including other patient responsibilities here, for example:

You play an important role in your treatment. Below is a list of things you can do to be an active participant in your treatment plan:

• Provide updated contact information.
• Notify us immediately of any changes in your insurance.
• Keep scheduled appointments and notify us as soon as possible if you need to change an appointment (insert practice policy regarding appointment changes or cancellations).
• Respond promptly to requests from the practice or others such as a specialty pharmacy, to avoid treatment delays.
• Maintain symptom diaries or other information requested by your provider.

Contacting Us

Consider providing names and contact information for appropriate team members to ensure patients can reach the appropriate person(s) in the practice.

Frequently Asked Questions

In this section, consider providing a list of commonly asked questions received by staff members.

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 or for Detrusor Overactivity Associated With a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX® for spasticity or detrusor overactivity associated with a neurologic condition should be monitored closely.

Please see additional Important Safety Information about BOTOX® on following pages.
warnings and precautions (continued)

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX® (onabotulinumtoxinA) (3% at 251 Units to 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%).
IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

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

Autonomic dysreflexia associated with intradetrusor injections of BOTOX® (onabotulinumtoxinA) 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).

Urinary Tract Infections in Patients With Overactive Bladder

BOTOX® increases the incidence of urinary tract infection. 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.

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

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.

Overactive Bladder
In clinical trials, 6.5% of patients (36/552) initiated clean intermittent catheterization for urinary retention following treatment with BOTOX® (onabotulinumtoxinA) 100 Units as compared to 0.4% of patients (2/542) treated with placebo. The median duration of catheterization for patients treated with BOTOX® 100 Units was 63 days (minimum 1 day to maximum 214 days) as compared to a median duration 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

Please see additional Important Safety Information about BOTOX® on following pages.
Urinary Retention in Patients Treated for Bladder Dysfunction (continued)

Overactive Bladder (continued)

Patients with diabetes mellitus treated with BOTOX® (onabotulinumtoxinA) were more likely to develop urinary retention than nondiabetics. In clinical trials, 12.3% of patients (10/81) with diabetes developed urinary retention following treatment with BOTOX® 100 Units vs 0% patients (0/69) treated with placebo. In patients without diabetes, 6.3% of patients (33/526) developed urinary retention following treatment with BOTOX® 100 Units vs 0.6% of patients (3/516) treated with placebo.

Detrusor Overactivity Associated With a Neurologic Condition

In clinical trials, 30.6% of patients (33/108) who were not using clean intermittent catheterization (CIC) prior to injection, required catheterization for urinary retention following treatment with BOTOX® 200 Units as compared to 6.7% of patients (7/104) treated with placebo. The median duration of post-injection catheterization for these patients treated with BOTOX® 200 Units (n = 33) was 289 days (minimum 1 day to maximum 530 days) as compared to a median duration of 358 days (minimum 2 days to maximum 379 days) for patients receiving placebo (n = 7).

Among patients not using CIC at baseline, those with multiple sclerosis (MS) were more likely to require CIC post-injection than those with spinal cord injury (SCI).

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

ADVERSE REACTIONS

Adverse reactions to BOTOX® (onabotulinumtoxinA) for injection are discussed in greater detail in the following sections: Boxed Warning, Contraindications, and Warnings and Precautions.

Overactive Bladder
The most frequently reported adverse reactions for overactive bladder occurring within 12 weeks of injection include urinary tract infection (BOTOX® 18%, placebo 6%), dysuria (BOTOX® 9%, placebo 7%), urinary retention (BOTOX® 6%, placebo 0%), bacteriuria (BOTOX® 4%, placebo 2%), and residual urine volume (BOTOX® 3%, placebo 0%).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX® 100 Units and placebo than non-diabetics. The incidence of UTI increased in patients who experienced a maximum post-voidal (PVR) urine volume ≥ 200 mL following BOTOX® injection compared to those with a maximum PVR < 200 mL following BOTOX® injection, 44% vs 23%, respectively.

Detrusor Overactivity Associated With a Neurologic Condition
The most frequently reported adverse reactions within 12 weeks of BOTOX® injection for detrusor overactivity associated with a neurologic condition include urinary tract infection (BOTOX® 24%, placebo 17%), urinary retention (BOTOX® 17%, placebo 3%), and hematuria (BOTOX® 4%, placebo 3%).

The following adverse event rates were reported at any time following initial injection and prior to reinjection 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%).

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

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%).

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® or other agents interfering with neuromuscular transmission (eg, aminoglycosides, 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®.

For more information on BOTOX®, please see the accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

Reference:
1. BOTOX® (onabotulinumtoxinA) Prescribing Information, April 2017.
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
• Warnings and Precautions (5.5, 5.7, 5.13, 5.14) 4/2017

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

Important Limitations: Safety and effectiveness of BOTOX have not been established for:
• Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)
• Treatment of upper or lower limb spasticity in pediatric patients (1.3)
• Treatment of hyperhidrosis in body areas other than axillary (1.5)

DOSEAGE AND ADMINISTRATION
Follow indication-specific dosage and administration recommendations; Do not exceed a total dose of 400 Units administered in a 3 month interval (2.1)
See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)
Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)
Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)
Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.4)
Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.5)
Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)
Cervical Dystonia: Base dosing on the patient’s head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naive patients (2.6)

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

CONTRAINDICATIONS
• Potency Units of BOTOX are 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)
• Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
• Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
• Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
• Urinary tract infections in patients treated for OAB (5.12)
• Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or 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)

USES 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: 4/2017
3 DOSE 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 Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition

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

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.3 Post-Marketing Experience

**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 asthma, 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. [See Warnings and Precautions (5.2)]

1 INDICATIONS AND USAGE

1.1 Bladder Dysfunction

1.1.1 Overactive Bladder

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

1.1.2 Detrusor Overactivity associated with a Neurologic Condition

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

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

1.3 Spasticity

1.3.1 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).

1.3.2 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).

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see Warnings and Precautions (5.1) and Description (11)].

Indication-specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3 month interval.

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.

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 Lactation

8.3 Pediatric Use

8.4 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

14.2 Detrusor Overactivity associated with a Neurologic Condition

14.3 Chronic Migraine

14.4 Spasticity

14.5 Cervical Dystonia

14.6 Primary Axillary Hyperhidrosis

14.7 Blepharospasm

14.8 Strabismus

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
2.2 Preparation and Dilution Technique

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

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

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

* Preservative-free 0.9% Sodium Chloride Injection, USP Only
** For Detrusor Overactivity associated with a Neurologic Condition see Section 2.3

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

An injection of BOTOX is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile needle and syringe should be used to enter the vial on each occasion for removal of BOTOX. Reconstituted BOTOX should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

2.3 Bladder Dysfunction

General

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

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

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection. The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL. Complete the reconstitution by adding 8 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in 30 mL syringes each containing 10 mL (~67 Units 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.
- 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 30 mL syringes each containing 10 mL (~67 Units each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

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

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

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

2.4 Chronic Migraine

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

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose (Number of Sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis†</td>
<td>20 Units divided in 4 sites</td>
</tr>
<tr>
<td>Corrugator†</td>
<td>10 Units divided in 2 sites</td>
</tr>
<tr>
<td>Procerus†</td>
<td>5 Units in 1 site</td>
</tr>
<tr>
<td>Occipitalis†</td>
<td>30 Units divided in 6 sites</td>
</tr>
<tr>
<td>Temporalis†</td>
<td>40 Units divided in 8 sites</td>
</tr>
<tr>
<td>Trapezius†</td>
<td>30 Units divided in 6 sites</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group†</td>
<td>20 Units divided in 4 sites</td>
</tr>
<tr>
<td><strong>Total Dose:</strong></td>
<td><strong>155 Units divided in 31 sites</strong></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 may be useful.

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

**Upper Limb Spasticity**

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

**Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity**

<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>

**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>

**2.6 Cervical Dystonia**

A double-blind, placebo-controlled study enrolled patients who had extended histories of receiving and tolerating BOTOX injections, with prior individualized adjustment of dose. The mean BOTOX dose administered to patients in this study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The BOTOX dose was divided among the affected muscles [see Clinical Studies (14.5)].

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

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL, with preservative-free 0.9% Sodium Chloride Injection, USP, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 1). In general, no more than 50 Units per site should be administered using a sterile needle (e.g., 25-30 gauge) of an appropriate length. Localization of the involved muscles with electromyographic guidance may be useful.
Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the double-blind, placebo-controlled study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.7 Primary Auxiliary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor’s Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 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 bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject BOTOX directly through the ink mark to avoid a permanent tattoo effect.

2.8 Blepharospasm

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

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

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

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

2.9 Strabismus

BOTOX is intended for injection into extraculcular 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. Dose 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

Intraderm injection of BOTOX is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection. Intraderm 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 product assessed with any 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. Symptoms of the systemic spread of BOTOX may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity 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 suspicious symptoms 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) or severe primary auxiliary 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 known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX [see Warnings and Precautions (5.2, 5.6)].

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)].

5.6 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)].

Differences from placebo were not statistically significant.

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 FVC ≤ 0.75), the event rate in change of Forced Vital Capacity (FVC) ≥15% or >20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 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 FVC From Baseline at Week 1, 6, 12 Post-injection with Up to Two Treatment Cycles with BOTOX or Placebo

<table>
<thead>
<tr>
<th>Week 1</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>4%</td>
<td>0%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>10%</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Differences from placebo were not statistically significant.

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

5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus
During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

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

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

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

In patients who are not catheterizing, 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 6: Number and Percent of Patients Experiencing at Least a 15% or 20% Decrease in FVC From Baseline at Week 2, 6, 12 Post-injection with BOTOX or Placebo

<table>
<thead>
<tr>
<th>Week 2</th>
<th>≥15%</th>
<th>≥20%</th>
<th>≥15%</th>
<th>≥20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/15 (0%)</td>
<td>1/11 (9%)</td>
<td>0/11 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 6</th>
<th>≥15%</th>
<th>≥20%</th>
<th>≥15%</th>
<th>≥20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/13 (15%)</td>
<td>1/13 (8%)</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 12</th>
<th>≥15%</th>
<th>≥20%</th>
<th>≥15%</th>
<th>≥20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/12 (0%)</td>
<td>0/7 (0%)</td>
<td>0/7 (0%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 8.

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

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Placebo</th>
<th>Patients with Diabetes</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units (N=552)</td>
<td>Placebo (N=542)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>12.3% (n=10)</td>
<td>0% (n=3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.3% (n=33)</td>
<td>0.6% (n=3)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with diabetes mellitus treated with BOTOX were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 10).

Table 10: Proportion of Patients by Etiology (MS and SCI) Not Using CIC at Baseline and then Catheterizing for Urinary Retention Following an Injection in Double-blind, Placebo-controlled Clinical Trials

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BOTOX 200 Units (N=86)</th>
<th>Placebo (N=88)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At any time during complete treatment cycle</td>
<td>31% (n=27)</td>
<td>5% (n=4)</td>
</tr>
<tr>
<td>Min, Max</td>
<td>1,530</td>
<td>2,379</td>
</tr>
</tbody>
</table>

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

5.14 Human Albumin and Transmission of Viral Diseases
This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

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

- Spread of Toxin Effects [see Warnings and Precautions (5.2)]
- Serious Adverse Reactions with Unapproved Use [see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions [see Contraindications (5.4) and Warnings and Precautions (5.4)]
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders [see Warnings and Precautions (5.5)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status [see Warnings and Precautions (5.7)]
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm [see Warnings and Precautions (5.8)]
- Retropulbar Hemorrhages in Patients Treated with BOTOX for Strabismus [see Warnings and Precautions (5.9)]
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity [see Warnings and Precautions (5.10)]
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated with a Neurologic Condition [see Warnings and Precautions (5.11)]
- Urinary Tract Infections in Patients with Overactive Bladder [see Warnings and Precautions (5.12)]
- Urinary Retention in Patients Treated for Bladder Dysfunction [see Warnings and Precautions (5.13)]

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

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

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

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin [see Warnings and Precautions (5.2)].

Overactive Bladder
Table 11 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 11: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Often than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-blind, Placebo-controlled Clinical Trials in Patients with OAB

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

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

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 12.
The incidence of UUT in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX injection was compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

Detrusor Overactivity associated with a Neurologic Condition

Table 13 presents the most frequently reported adverse reactions in the two Phase 3 double-blind, placebo-controlled studies (NDO-1 and NDO-2) within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX 200 Units.

Table 13: Adverse Reactions Reported by ≤2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection in Double-blind, Placebo-controlled Clinical Trials (NDO-1 and NDO-2)

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

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

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

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

Table 14 presents the most frequently reported adverse reactions in a placebo-controlled, double-blind post-approval 52-week study with BOTOX 100 Units (Study NDO-3) conducted in MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and not catheterized at baseline. The table below presents the most frequently reported adverse reactions within 12 weeks of injection.

Table 14: 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 (NDO-3)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX (N=66)</th>
<th>Placebo (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>17 (26%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Bacteriuria</td>
<td>6 (9%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>10 (15%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>3 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Residual urine volume*</td>
<td>11 (17%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

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

The following adverse events with BOTOX 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 51 weeks): urinary tract infections (39%), bacteriuria (18%), urinary retention (17%), gait disorder (17%), residual urine volume* (17%), dysuria (9%), and hematuria (5%).

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

Chronic Migraine

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

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 15.

Table 15: Adverse Reactions Reported by ≤2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX (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 paresthesia</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (3%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (9%)</td>
<td>19 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (3%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>23 (3%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (2%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

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

Upper Limb Spasticity

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

Table 16: Adverse Reactions Reported by ≤2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trials

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

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

Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 17. 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 17: Adverse Reactions Reported by ≤2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)

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

Cervical Dystonia
In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphoria (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, hypotension, weakness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dysphoria have been reported.

Dysphoria 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 dysphoria with about 20% of these cases also reporting dyspnea [see Warnings and Precautions (5.2, 5.6)]. Most dysphoria is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms [see Warnings and Precautions (5.2, 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.

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

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

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

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

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

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

In duodenal overactivity associated with neurologic condition patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to BOTOX in the remaining 2 patients is not known.

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

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

6.3 Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia; including macaradosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; hyperhidrosis; hypoaesthesia; hypoaesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasis vulgaris; arthropathy; trinitus; 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 BOTOX [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 exaggerated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

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

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Bladder Dysfunction

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

Prophylaxis of Headaches in Chronic Migraine

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

Spasticity

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

Auxiliary Hyperhidrosis

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

Cervical Dystonia

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

Blepharospasm and Strabismus

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

8.5 Geriatric Use

Of the 2145 patients in placebo-controlled clinical studies of BOTOX for the treatment of spasticity, 33.5% were 65 or older, and 7.7% were 75 years of age or older. No overall differences in safety were observed between elderly patients and younger patients. In clinical studies of BOTOX across other indications, no overall differences in safety were observed between elderly patients and younger patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% were 65 years of age or older, and 14.7% were 75 years of age or older. Adverse reactions of UI 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 18). 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 18: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>≤65 Years (%)</th>
<th>65 to 74 Years (%)</th>
<th>&gt;75 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>73 (21%)</td>
<td>23 (7%)</td>
<td>51 (30%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>21 (6%)</td>
<td>2 (0.6%)</td>
<td>14 (8%)</td>
</tr>
</tbody>
</table>

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

10 OVERDOSAGE

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

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

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

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mmr5292a6.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 and intradural use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride in a sterile, vacuum-dried form without a preservative.

Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride; or 200 Units 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 autonomic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX.

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

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males; 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 5 Units/kg in females) are approximately equal to the human dose of 400 Units on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

Two double-blind, placebo-controlled, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (N=557), or placebo (N=548). Patients received 20 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 19 and 20, and Figures 5 and 6.

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

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

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

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

** Primary timepoint

† Primary variable

§ Secondary variable

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

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

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

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

** Primary timepoint

† Primary variable

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

14.2 Detrusor Overactivity associated with a Neurologic Condition

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 21 and 22, and Figures 7 and 8. No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.
The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

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

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX (100 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 23.

### Table 23: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH\textsubscript{2}O) in Study NDO-3

<table>
<thead>
<tr>
<th>Variable</th>
<th>BOTOX 100 Units (N=347)</th>
<th>Placebo (N=358)</th>
<th>Treatment Difference*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Frequency of Urinary Incontinence Episodes\textsuperscript{a}</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>66</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>4.2</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-29.1</td>
<td>-1.2</td>
<td>-1.7</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6\textsuperscript{b}</td>
<td>-3.4</td>
<td>-1.1</td>
<td>-2.3 (-3.0, -1.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-2.7</td>
<td>-1.0</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity\textsuperscript{b} (mL)</strong></td>
<td>134.4</td>
<td>3.5</td>
<td>130.9 (94.8, 167.0)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>248.9</td>
<td>245.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6\textsuperscript{b}</td>
<td>-19.2</td>
<td>2.7</td>
<td>-21.9 (-37.5, -6.5)</td>
<td></td>
</tr>
</tbody>
</table>

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

\textsuperscript{a} Primary endpoint

\textsuperscript{b} Secondary endpoint

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

### 14.3 Chronic Migraine

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

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

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

* Significantly different from placebo (p<0.05)
The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 26.

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

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

1 Primary endpoint at Week 6  
2 Secondary endpoints at Week 6  
3 Significantly different from placebo (p≤0.05)  
4 BOTOX injected into both the flexor carpi radialis and ulnaris muscles  
5 BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles  
6 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 27).

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Total Dose</th>
<th>Injection Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>BOTOX (90 Units)</td>
<td>BOTOX (180 Units)</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>10 Units</td>
<td>20 Units</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>15 Units</td>
<td>30 Units</td>
</tr>
<tr>
<td>Finger</td>
<td>7.5 Units</td>
<td>15 Units</td>
</tr>
<tr>
<td>Flexor Digitorum Profundus</td>
<td>7.5 Units</td>
<td>15 Units</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>50 Units</td>
<td>100 Units</td>
</tr>
</tbody>
</table>

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

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 28.

### 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 and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 25). Use of an EMG nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

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

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

* injected only if spasticity is present in this muscle
Studied 4 included 170 patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units (N=21), BOTOX mid dose = 180 Units (N=23), BOTOX high dose = 360 Units (N=21) Follow-up in Study 4 was 12 weeks.

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

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 31. The MAS uses a similar scoring system as the Ashworth Scale.

Table 30: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
<th>Study 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX</td>
<td>Volume (mL)</td>
<td>BOTOX low dose (Units)</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>

†† Secondary endpoint at Week 6
* Significantly different from placebo (p<0.001)
††† BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function] are presented in Table 32.

Table 31: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

<table>
<thead>
<tr>
<th>Study 5</th>
<th>BOTOX (N=66)</th>
<th>Placebo (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale†††</td>
<td>-1.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>Median Physician Global Assessment of Response to Treatment††</td>
<td>2.0*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

†† Secondary endpoint at Week 6
* Significantly different from placebo (p<0.001)
††† BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Lower Limb Spasticity
The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 33) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.
Table 33: Study Medication Dose and Injection Sites in Study 6

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

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4 = very marked worsening to +4 = very marked improvement. Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 34).

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

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

* Significantly different from placebo (p<0.05)

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

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

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

14.5 Cervical Dystonia

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

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allot 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician’s evaluation of the patients’ status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 35.

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

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

* Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.

† These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.

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

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 36. The total dose and muscles selected were tailored to meet individual patient needs.

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

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Number of Patients Treated in This Muscle (N=88)</th>
<th>Mean % Dose per Muscle</th>
<th>Mid-Range of % Dose per Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleniens cervicis</td>
<td>83</td>
<td>38</td>
<td>25-50</td>
</tr>
<tr>
<td>Sternoclidomastoid</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>Scaleniens</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 not noticeable and never interferes with my daily activities”; 2 = “underarm sweating is noticeable and does not interfere with my daily activities”; 3 = “underarm sweating is noticeable and interferes with my daily activities”; 4 = “underarm sweating is noticeably intense and always interferes with my daily activities.”

A total of 322 patients were randomized to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection. Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat 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 37).

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

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

### Table 37: Study 1 - Study Outcomes

<table>
<thead>
<tr>
<th>Treatment Response</th>
<th>BOTOX 50 Units (N=104)</th>
<th>BOTOX 75 Units (N=110)</th>
<th>Placebo (N=108)</th>
<th>BOTOX 50-placebo (95% CI)</th>
<th>BOTOX 75-placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDSS Score change ≥2 (%)</td>
<td>55% (57)</td>
<td>49% (54)</td>
<td>6% (6)</td>
<td>49.3% (38.8, 59.7)</td>
<td>43% (33.2, 53.8)</td>
</tr>
<tr>
<td>&gt;50% decrease in axillary sweat production % (n)</td>
<td>81% (84)</td>
<td>86% (94)</td>
<td>41% (44)</td>
<td>40% (28.1, 52.0)</td>
<td>45% (33.9, 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 several studies, in an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of BOTOX at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks. One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

### 14.8 Strabismus

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

### 16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes: 100 Units 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.

### 17 PATIENT COUNSELING INFORMATION

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

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

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

**Ability to Operate Machinery or Vehicles**

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

**Voiding Symptoms after Bladder Injections**

After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.
What is the most important information I should know about BOTOX and BOTOX Cosmetic?

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

• Problems breathing or swallowing

• Spread of toxin effects

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

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

• People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with BOTOX or BOTOX Cosmetic.

• Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving BOTOX or BOTOX Cosmetic have the highest risk of getting these problems.

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

• loss of strength and muscle weakness all over the body

• double vision

• blurred vision and drooping eyelids

• hoarseness or change or loss of voice (dysphonia)

• trouble saying words clearly (dysarthria)

• loss of bladder control

• trouble breathing

• trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of BOTOX or BOTOX Cosmetic. These problems could make it unsafe for you to drive a car or do other dangerous activities. See “What should I avoid while receiving BOTOX or BOTOX Cosmetic?”

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

What are BOTOX and BOTOX Cosmetic?

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

• to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.

• to treat leakage of urine (incontinence) in adults with overactive bladder 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.
• had an allergic reaction to any other botulinum toxin product such as Myobloc®, Dysport®, or Xeomin®
• have a skin infection at the planned injection site
• are being treated for urinary incontinence and have a urinary tract infection (UTI)
• are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing)

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?
Tell your doctor about all your medical conditions, including if you:
• have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig’s disease], myasthenia gravis or Lambert-Eaton syndrome). See “What is the most important information I should know about BOTOX and BOTOX Cosmetic?”
• have allergies to any botulinum toxin product
• had any side effect from any botulinum toxin product in the past
• have or have had a breathing problem, such as asthma or emphysema
• have or have had swallowing problems
• have 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?
• BOTOX or BOTOX Cosmetic is an injection that your doctor will give you.
• BOTOX is injected into your affected muscles, skin, or bladder.
• BOTOX Cosmetic is injected into your affected muscles.
• Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.

What should I avoid while taking BOTOX or BOTOX Cosmetic?
BOTOX and BOTOX Cosmetic may cause loss of strength or general muscle weakness, 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.

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**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

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

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