

# Injection Workbook for **Chronic Migraine**

Guidance for identifying BOTOX<sup>®</sup> candidates, the injection procedure, and discussing treatment with patients

## **Indication**

### **Chronic Migraine**

BOTOX<sup>®</sup> for injection is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine ( $\geq 15$  days per month with headache lasting 4 hours a day or longer).

## **Limitations of Use**

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.

## **IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING**

### **WARNING: DISTANT SPREAD OF TOXIN EFFECT**

Postmarketing reports indicate that the effects of BOTOX<sup>®</sup> 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 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<sup>®</sup> on following pages.

# Introduction

Take the next step in your education with this comprehensive guide to BOTOX® injections. Review Chronic Migraine diagnosis, anatomical assessment, injection technique, patient dialogue, and more.

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\*COMPEL = Chronic Migraine OnabotulinumtoxinA Prolonged Efficacy open Label.

†PREEMPT = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy.

## IMPORTANT SAFETY INFORMATION (continued)

### CONTRAINDICATIONS

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

### WARNINGS AND PRECAUTIONS

#### 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 dose have been reported.



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### **IMPORTANT SAFETY INFORMATION (continued)**

#### **WARNINGS AND PRECAUTIONS (continued)**

##### **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.

Migraine is a common, disabling primary headache disorder<sup>1,\*</sup>

Migraine is the  
**2nd**

leading cause of years lived with disability<sup>2,†</sup>

A day with a severe migraine attack  
is as disabling as a day lived with  
**active psychosis** or **quadriplegia**<sup>3</sup>

<sup>\*</sup>As defined in the ICHD-3.

<sup>†</sup>After back pain, according to the 2016 Global Burden of Diseases, Injuries, and Risk Factors Study.

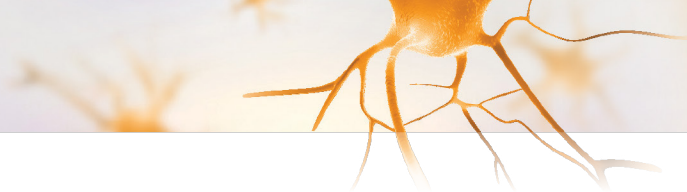
**IMPORTANT SAFETY INFORMATION (continued)**

**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.





|                            | Migraine Without Aura   | Migraine With Aura  |
|----------------------------|---|---|
| <b>Description</b>         | Recurrent headache disorder manifesting in attacks lasting 4-72 hours   | Recurrent attacks of fully reversible aura symptoms that are usually followed by headache and associated migraine symptoms  |
| <b>Diagnostic Criteria</b> | <p>A. At least 5 attacks fulfilling criteria B-D</p> <p>B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)</p> <p>C. Headache has at least 2 of the following 4 characteristics:</p> <ol style="list-style-type: none"> <li>1. Unilateral location</li> <li>2. Pulsating quality</li> <li>3. Moderate or severe pain intensity</li> <li>4. Aggravation with physical activity</li> </ol> <p>D. During headache at least 1 of the following:</p> <ol style="list-style-type: none"> <li>1. Nausea and/or vomiting</li> <li>2. Photophobia and phonophobia</li> <li>3. Not better accounted for by another ICHD-3 diagnosis</li> </ol> | <p>A. At least 2 attacks fulfilling criteria B-D</p> <p>B. One or more of the following fully reversible aura symptoms:</p> <ol style="list-style-type: none"> <li>1. Visual</li> <li>2. Sensory</li> <li>3. Speech and/or language</li> <li>4. Motor</li> <li>5. Brainstem</li> <li>6. Retinal</li> </ol> <p>C. At least 3 of the following 6 characteristics:</p> <ol style="list-style-type: none"> <li>1. At least 1 aura symptom spreads gradually over <math>\geq 5</math> minutes</li> <li>2. Two or more aura symptoms occur in succession</li> <li>3. Each individual aura symptom is unilateral</li> <li>4. At least 1 aura symptom is positive</li> <li>5. The aura is accompanied, or followed within 60 minutes, by headache</li> </ol> <p>D. Not better accounted for by another ICHD-3 diagnosis</p> |

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

**Hypersensitivity Reactions**

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

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

## Chronic Migraine is a progressive, distinct disease

### Practical clinical criteria<sup>4,5</sup>



### Important considerations<sup>1</sup>

- Count days when a headache lasted fewer than 4 hours due to a successful acute treatment
- Criteria must be met for 3 months per the ICHD-3
  - Patients receive a diagnosis according to the headache frequency that they currently present or that they have presented within the last year

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

##### **Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders**

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, 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*).



## A disease with distinct characteristics<sup>6-10</sup>

|   | Chronic Migraine   | Episodic Migraine                   |
|---|--|-------------------------------------|
| <b>Definition</b>   | <b>≥ 15 headache days per month;<br/>≥ 8 headache days are associated with<br/>migraine; ≥ 4 hours of headache per day</b> | <b>≤ 14 headache days per month</b> |
| <b>Average headache duration per<br/>attack (without medication)*</b> | <b>65.1 hours</b>  | <b>38.8 hours</b>                   |
| <b>MIDAS Grade IV (≥ 21)<sup>†</sup></b>                              | <b>79.1%</b>   | <b>23.6%</b>                        |
| <b>Visit emergency room*</b>  | <b>9.0% per year</b>   | <b>5.4% per year</b>                |
| <b>Anxiety<sup>‡,§</sup></b>  | <b>30.2%</b>   | <b>18.8%</b>                        |
| <b>Depression<sup>‡,§</sup></b>                                       | <b>41.2%</b>   | <b>25.6%</b>                        |
| <b>Obesity<sup>‡,§</sup></b>  | <b>25.5%</b>   | <b>21.0%</b>                        |

## Known risk factors for progression<sup>11-13</sup>

| Nonmodifiable                          | Modifiable                            |
|--|---------------------------------------|
| <b>Structural changes in the brain</b> | <b>Attack frequency</b>               |
| <b>Age</b>                             | <b>Obesity</b>                        |
| <b>Low education</b>                   | <b>Medication overuse</b>             |
| <b>Low socioeconomic status</b>        | <b>Inadequate symptomatic therapy</b> |
| <b>Head trauma</b>                     | <b>Caffeine overuse</b>               |
| <b>Sex</b>                             | <b>Snoring</b>                        |
| <b>Stress</b>                          | <b>Sleep apnea</b>                    |
| <b>Chronic pain</b>                    |                                       |
| <b>Depression/anxiety</b>              |                                       |

\*Chronic Migraine: n = 499; Episodic Migraine: n = 8227.

<sup>†</sup>MIDAS = The Migraine Disability Assessment Test.

<sup>‡</sup>Chronic Migraine: n = 655; Episodic Migraine: n = 11,249.

<sup>§</sup>Incidence of comorbidity.

### IMPORTANT SAFETY INFORMATION (continued)

#### WARNINGS AND PRECAUTIONS (continued)

##### Dysphagia and Breathing Difficulties

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

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

## The importance of a specific Chronic Migraine diagnosis

### Possible reasons clinicians may misdiagnose:

Patients did not accurately account for all their headache days

Classifying some migraine attacks as tension-type headaches, leading to a diagnosis of mixed headache disorder<sup>14</sup>

Not accounting for headache features, leading to an underdiagnosis of migraine days

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

##### **Human Albumin and Transmission of Viral Diseases**

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



## Getting to an appropriate diagnosis

1

### UNCOVER TRUE HEADACHE FREQUENCY

Ask about crystal clear  
(headache-free) days

Encourage patients to include  
postdrome as part of their  
headache day count

Ask how headache attacks are  
affecting the patient's daily life

Ask about  
migraine features

2

### CLEARLY COMMUNICATE A DIAGNOSIS

*"You have Chronic Migraine  
and you are not alone."*

OR

*"I believe that you have Chronic  
Migraine and it is having a significant  
impact on your life."*

#### IMPORTANT SAFETY INFORMATION (continued)

##### ADVERSE REACTIONS

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

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

## A structured approach to dialogue can help facilitate an appropriate diagnosis

### Key phrases to use during a Chronic Migraine assessment:

|                             |  |
|-----------------------------|--|
| <b>Headache frequency</b>   | <ul style="list-style-type: none"> <li>How many days per month do you <b>not</b> have headache?</li> </ul>   |
| <b>Extent of disability</b> | <ul style="list-style-type: none"> <li>How does your headache impact your life in work, family, and social settings?</li> <li>What is your headache keeping you from doing today?</li> <li>If you didn't have any responsibilities, what would you be doing on a migraine day?</li> </ul>  |
| <b>Migraine features</b>    | <ul style="list-style-type: none"> <li>Which type of migraine do you experience? <ul style="list-style-type: none"> <li><input type="checkbox"/> Migraine without aura   <input type="checkbox"/> Migraine with aura</li> </ul> </li> <li>What happens to you when you have a migraine attack? <ul style="list-style-type: none"> <li><input type="checkbox"/> Nausea   <input type="checkbox"/> Vomiting   <input type="checkbox"/> Light sensitivity   <input type="checkbox"/> Noise sensitivity</li> <li><input type="checkbox"/> Touch sensitivity   <input type="checkbox"/> Vision impairment   <input type="checkbox"/> Other</li> </ul> </li> <li>Can you describe all the symptoms of the migraine attacks you experience?</li> <li>Does taking acute medicine help to alleviate your symptoms?</li> </ul> |

#### IMPORTANT SAFETY INFORMATION (continued)

##### ADVERSE REACTIONS (continued)

##### Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), musculoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 0%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).

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 with 0.3% of placebo-treated patients.



The right communication style can help validate the patient's experience<sup>15</sup>

**The LEAP approach is one way to help clinicians alleviate migraine disease stigma to achieve a more open, productive dialogue**

| ACTION           | METHOD   | SAMPLE DIALOGUE  |
|------------------|--|--|
| <b>Listen</b>    | <ul style="list-style-type: none"> <li>• Employ active listening</li> <li>• Use a combination of open- and closed-ended questions</li> <li>• Elicit patient's agenda</li> </ul>    | <ul style="list-style-type: none"> <li>• <i>"What brings you here today?"</i></li> <li>• <i>"What worries or concerns do you have?"</i></li> <li>• <i>"Tell me more about that."</i></li> </ul>  |
| <b>Empathize</b> | <ul style="list-style-type: none"> <li>• Validate patient's experiences</li> <li>• Demonstrate concern for patient's distress</li> </ul>   | <ul style="list-style-type: none"> <li>• <i>"I believe that migraine is having a significant impact on your life."</i></li> <li>• <i>"I can see how it upsets you when people say that your migraine is just another headache."</i></li> </ul>   |
| <b>Accept</b>    | <ul style="list-style-type: none"> <li>• Be aware of how stigma can affect treatment</li> <li>• Accept the reality of the disease</li> </ul>                                       | <ul style="list-style-type: none"> <li>• <i>"Chronic Migraine is a debilitating disease that is often misunderstood."</i></li> </ul>   |
| <b>Partner</b>   | <ul style="list-style-type: none"> <li>• Educate</li> <li>• Set realistic goals together</li> <li>• Empower patient to take responsibility for their disease management</li> </ul> | <ul style="list-style-type: none"> <li>• <i>"How are you managing your disease?"</i></li> <li>• <i>"I understand that you want these symptoms to go away. There is no cure for Chronic Migraine yet, but if you could reduce the number of headache days, would that help?"</i></li> </ul> |

**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS (continued)**

**Postmarketing Experience**

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

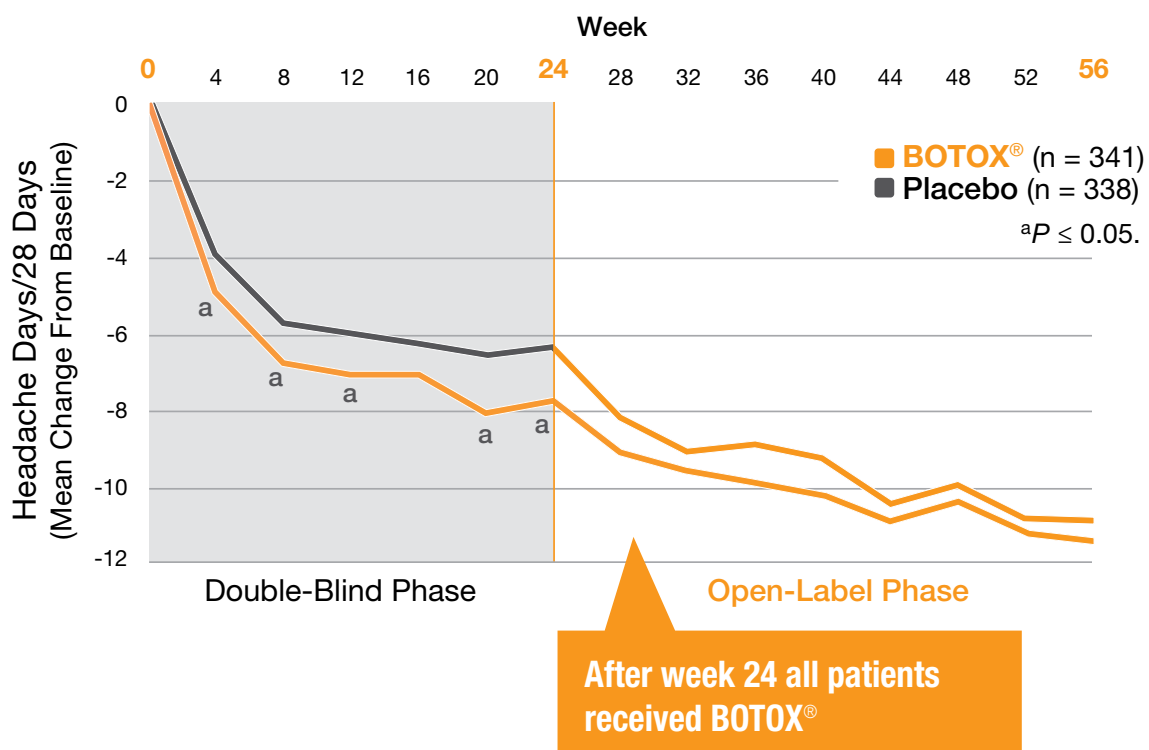
**Please see additional Important Safety Information about BOTOX® on following pages.**



## BOTOX<sup>®</sup> efficacy was achieved following the proven PREEMPT Paradigm

**Patients on BOTOX<sup>®</sup> had 8 to 9 fewer headache days and migraine/probable migraine days per month compared with baseline (vs 6 to 7 days with placebo) at 24 weeks**<sup>5,16,17</sup>

### RESULTS FROM PREEMPT 1<sup>5,16</sup>



**Study design:** PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Subjects included adult Chronic Migraine patients not using any concurrent headache prophylaxis and, during a 28-day baseline period, had  $\geq 15$  headache days lasting 4 hours or more, with  $\geq 50\%$  being migraine/probable migraine. Patients were allowed to use acute headache treatments during the study. Primary end point was 24 weeks.

**DIALOGUE TIP:** “BOTOX<sup>®</sup> results were based on patients receiving 2 treatments, 12 weeks apart. If you don’t get treated every 12 weeks, then you may not get the **full benefit** of the treatment.”<sup>5</sup>

#### IMPORTANT SAFETY INFORMATION (continued)

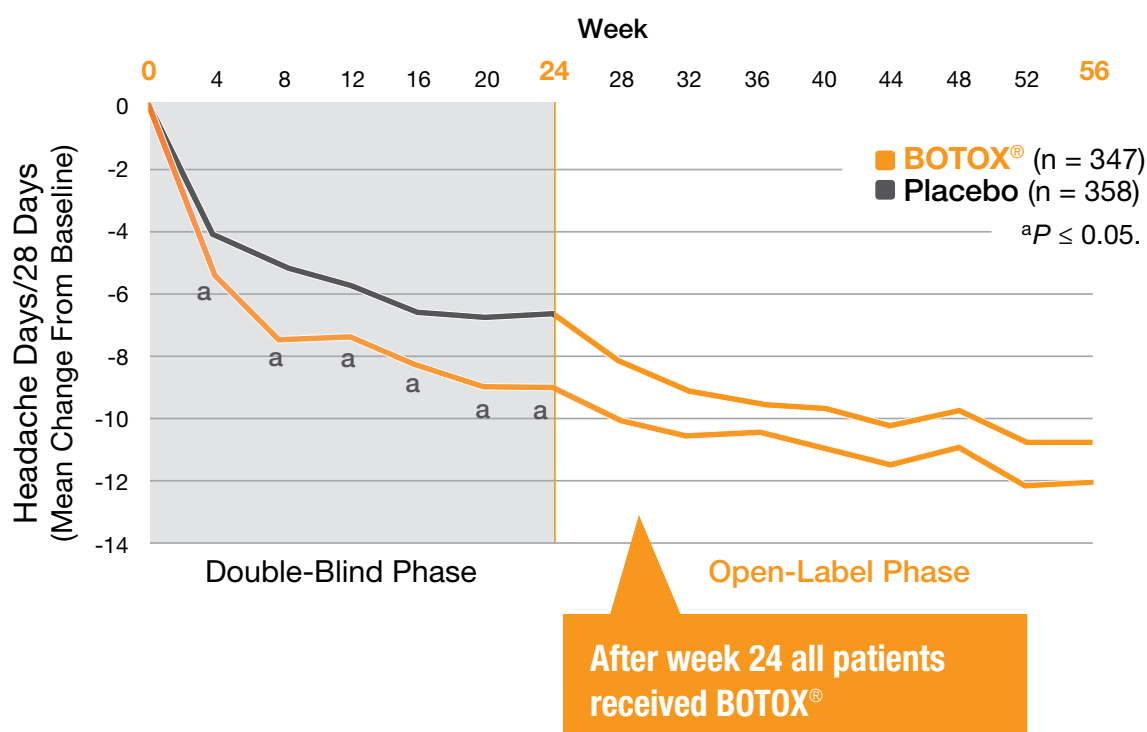
##### ADVERSE REACTIONS (continued)

##### Postmarketing Experience (continued)

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.

**Patients on BOTOX® had 8 to 9 fewer headache days and migraine/probable migraine days per month compared with baseline (vs 6 to 7 days with placebo) at 24 weeks<sup>5,16,17</sup>**

## RESULTS FROM PREEMPT 2<sup>5,17</sup>



**The PREEMPT Paradigm calls for injections in 31 sites across 7 head/neck muscle areas, with a total dose of 155 Units.<sup>5</sup>**

### IMPORTANT SAFETY INFORMATION (continued) DRUG INTERACTIONS

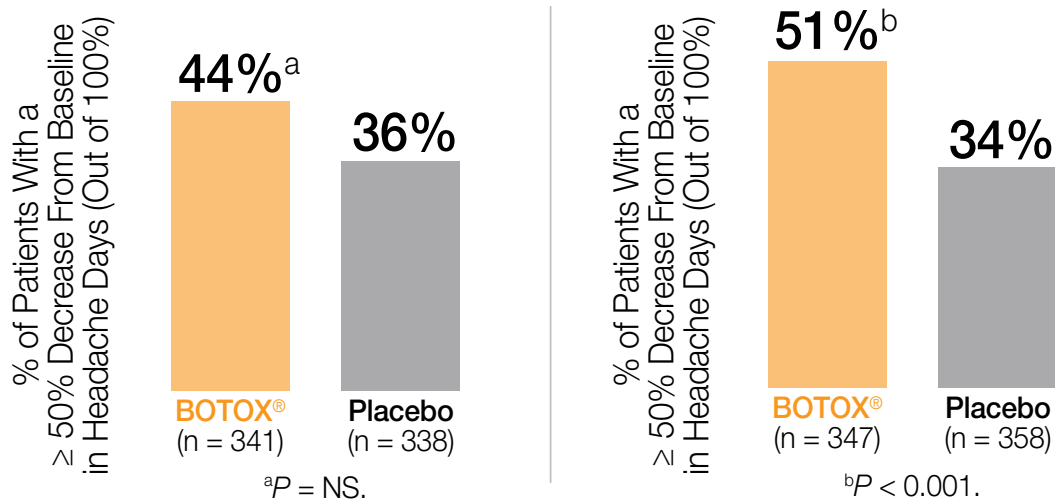
Co-administration of BOTOX® and other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic 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®.

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

## Responder rates for BOTOX<sup>®</sup> patients in PREEMPT clinical trials

**50%** reduction in headache days from baseline in each month at week 24<sup>18,19</sup>

### RESULTS FROM PREEMPT 1      RESULTS FROM PREEMPT 2



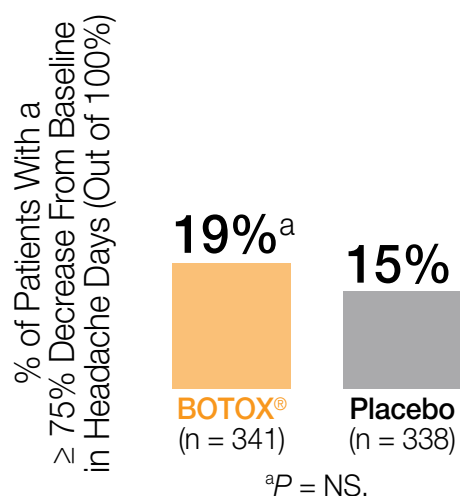
**Significant difference in BOTOX<sup>®</sup> vs placebo in PREEMPT 2 but not PREEMPT 1.**

- Responder rate data based on “Other” end point in PREEMPT clinical trials

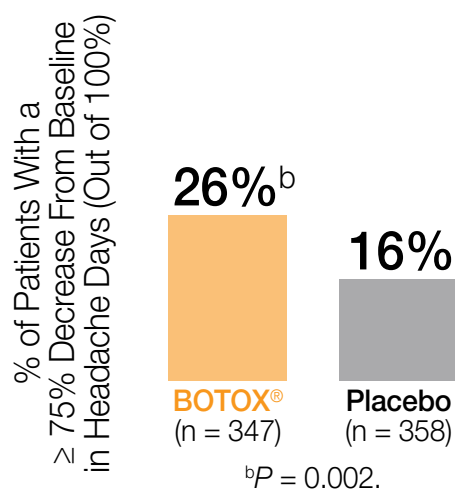
**Study design:** PREEMPT 1 and 2 were randomized, double-blind, placebo-controlled studies (N = 1384) across 122 sites. Primary time point was 24 weeks. Subjects included adult Chronic Migraine patients, who in a 28-day baseline period had at least 15 headache days lasting 4 hours or more, with at least 50% being migraine/probable migraine.

**75%** reduction in headache days from baseline in each month at week 24<sup>18,19</sup>

## RESULTS FROM PREEMPT 1



## RESULTS FROM PREEMPT 2



Significant difference in BOTOX® vs placebo in PREEMPT 2 but not PREEMPT 1.

- Responder rate data based on “Other” end point in PREEMPT clinical trials

### 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 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.

## Adverse events observed during PREEMPT pivotal trials<sup>5</sup>

### Adverse reactions $\geq 5\%$ in Chronic Migraine clinical trials were headache and neck pain (n = 687)

Adverse reactions reported by  $\geq 2\%$  of patients treated with BOTOX<sup>®</sup> and more frequent than in placebo-treated patients in 2 Chronic Migraine double-blind, placebo-controlled trials.

| Adverse Reactions   | BOTOX <sup>®</sup><br>155 Units to<br>195 Units<br>(n = 687)<br>% | Placebo<br>(n = 692)<br>% |
|---|---|---------------------------|
| <b>Nervous system disorders</b>                             |   |                           |
| Headache  | 5   | 3                         |
| Migraine  | 4   | 3                         |
| Facial paresis  | 2   | 0                         |
| <b>Eye disorders</b>  |   |                           |
| Eyelid ptosis   | 4   | < 1                       |
| <b>Infections and infestations</b>                          |   |                           |
| Bronchitis  | 3   | 2                         |
| <b>Musculoskeletal and connective tissue disorders</b>      |   |                           |
| Neck pain   | 9   | 3                         |
| Musculoskeletal stiffness                                   | 4   | 1                         |
| Muscular weakness   | 4   | < 1                       |
| Myalgia   | 3   | 1                         |
| Musculoskeletal pain  | 3   | 1                         |
| Muscle spasms   | 2   | 1                         |
| <b>General disorders and administration-site conditions</b> |   |                           |
| Injection-site pain   | 3   | 2                         |
| <b>Vascular disorders</b>                                   |   |                           |
| Hypertension  | 2   | 1                         |

- 4% of BOTOX<sup>®</sup> patients discontinued pivotal trials due to adverse events (vs 1% for placebo)
- Observed treatment-related adverse events were typically mild to moderate in severity

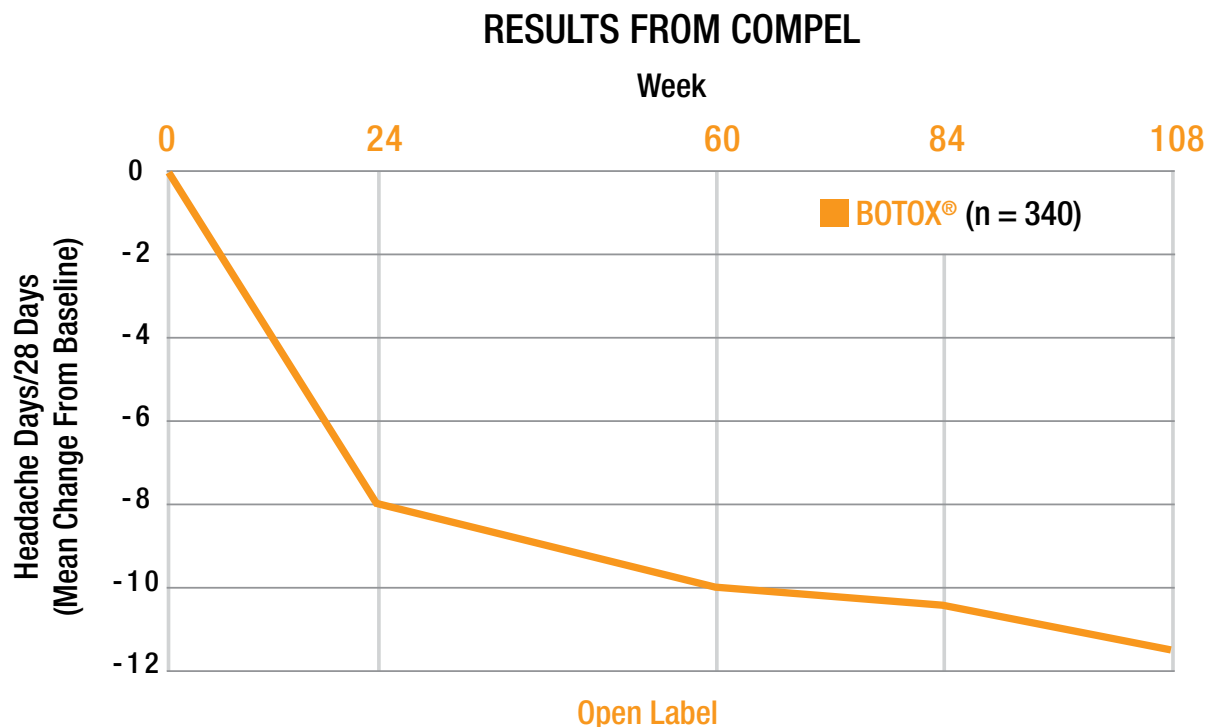
**DIALOGUE TIP:** “The **most common BOTOX<sup>®</sup>** side effect was neck pain, which was experienced by 9 out of 100 patients (vs 3 out of 100 for placebo).”<sup>5</sup>

#### IMPORTANT SAFETY INFORMATION (continued) CONTRAINDICATIONS

BOTOX<sup>®</sup> is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

## Results from the 2-year, open-label COMPEL trial<sup>20-22</sup>

**Efficacy consistent with PREEMPT trials over 108 weeks and up to 9 treatments**



- 8.0, 10.0, 10.5, and 11.6 fewer headache days per month from baseline at weeks 24, 60, 84, and 108, respectively
- Data from the subgroup of patients who did not use an oral preventive medication anytime during the study are presented (n = 340)
- Adverse events from the COMPEL trial were consistent with those from the PREEMPT trials

**Study design:** Open-label study (n = 716) in which enrolled patients received 155 units of BOTOX® (31 sites in a fixed-site, fixed-dose paradigm across 7 head/neck muscles over 12 weeks for 9 treatment cycles [108 weeks]). The primary end point was headache-day reduction at week 108. 56% of patients enrolled received all 9 treatments, and 52% received all study treatments and attended the final follow-up visit.

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

#### **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 dose have been reported.

#### **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.**

## PREEMPT Paradigm overview

**The PREEMPT Paradigm is based on 10 years of studies to assess patient type, muscle selection, dose, and treatment interval<sup>23-32</sup>**

**155**  
**UNITS**

**PROVEN DOSE**

155 Units<sup>5</sup>

**12**  
**WEEKS**

**PROVEN SCHEDULE**

Trial of 2 treatments, 12 weeks apart, with further retreatment every 12 weeks<sup>5,\*</sup>

**31**  
**SITES**

**PROVEN SITES**

31 sites across 7 specific head and neck muscle areas<sup>5</sup>

\*Retreatment after 24 weeks should be determined per clinician's discretion.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**



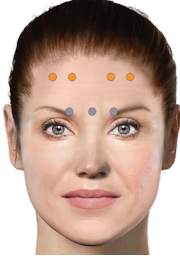

**Serious Adverse Reactions With Unapproved Use**

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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. The safety and effectiveness of BOTOX<sup>®</sup> for unapproved uses have not been established.








## Summary of dose by area<sup>5</sup>

|   |   |  |   |
|---|---|--|---|
|  |  |  |  |
| <b>Corrugator</b><br>10 Units divided in 2 sites                                  | <b>Procerus</b><br>5 Units in 1 site  | <b>Frontalis</b><br>20 Units divided in 4 sites                                    | <b>Temporalis</b><br>40 Units divided in 8 sites                                    |

---

|  |   |  |
|--|---|--|
|  |  |  |
| <b>Occipitalis</b><br>30 Units divided in 6 sites                                  | <b>Cervical paraspinals</b><br>20 Units divided in 4 sites                          | <b>Trapezius</b><br>30 Units divided in 6 sites                                      |

**TOTAL DOSE: 155 Units divided between 31 sites\***

\*Document and discard the 45-Unit wastage.

The following section provides a step-by-step overview of the PREEMPT Paradigm for BOTOX®. Departures from the approved paradigm may lead to efficacy results and adverse events different from those seen in the clinical trials.

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

#### **Hypersensitivity Reactions**

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

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

## General injection considerations

### STANDARD METHODS REGARDLESS OF AREA

- For each injection, the **injection volume will be 0.1 mL** (equivalent to 5 Units)<sup>5</sup>
- **Consider injecting** in the most superficial aspect of the muscle
- **Evaluate the anatomy**, including relevant function and the effects of treatment on these muscles
- **Recognize unique anatomy**, as no 2 patients are alike; focus on the muscle, not measurements, to adjust for individual anatomical variations
- **Consider location, depth, and angle carefully**, as the site of medication delivery may be different from the needle insertion point
  - Injection sites depicted in diagrams represent the delivery point of the medication

### BEFORE INJECTION

- **Verify the needle is securely fastened** to the injection syringe
- **Line up the bevel of the needle** with the gradations on the syringe so the bevel is facing upward; this will help you more easily orient the bevel of the needle when injecting

#### IMPORTANT SAFETY INFORMATION (continued)

#### WARNINGS AND PRECAUTIONS (continued)

##### Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, 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*).



## DURING INJECTION

- **Inject on 1 side first for bilateral injections**, then proceed to the other side and repeat
- **Consider changing needles frequently** to reduce patient discomfort; consider using 1 needle per area or changing every 4 to 6 sites
- **Inject with the bevel up**, pointing away from the skin
- It may be helpful to **hold the hub of the needle with 1 hand** to ensure the needle does not twist
  - Push the plunger with the other hand to administer the medication
- **Aspirate** to ensure no blood return
- **Target the muscle**—The needle should be inserted through the epidermis/dermis layer, which may feel more rigid when penetrated. The injection should be given just when there is a decrease in resistance, avoiding the periosteum. This decrease in resistance may be subdermal, not intramuscular

### 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*).

##### Human Albumin and Transmission of Viral Diseases

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

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

## Anterior injections\*

### Anatomy of the face and head

#### Frontalis

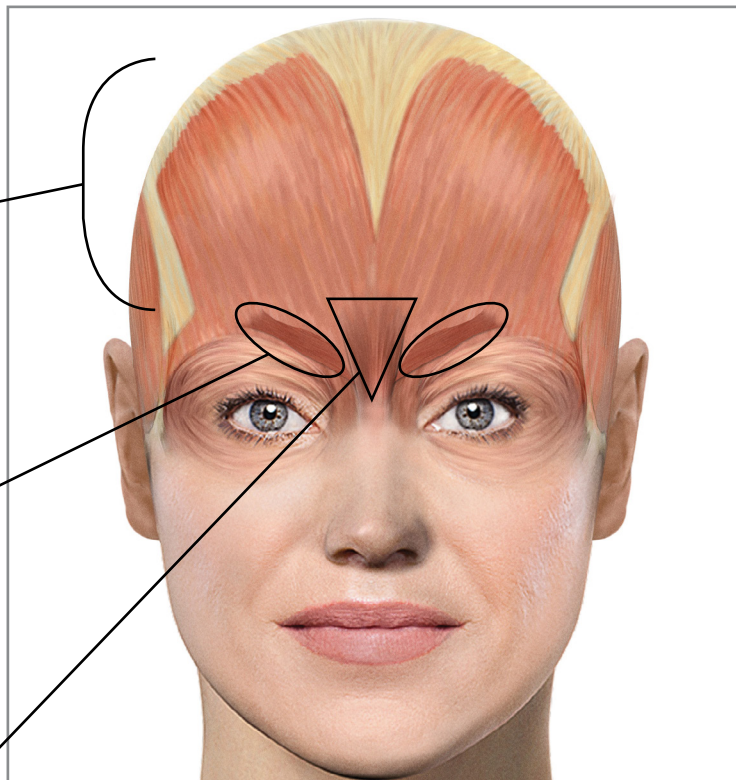
Originates from the epicranial aponeurosis, and attaches distally to the skin of the forehead and eyebrow<sup>32,33</sup>

#### Corrugator

Attaches to the nasal-frontal bone medially and the skin of the eyebrow laterally<sup>32-34</sup>

#### Procerus

Originates from the aponeurotic fascia of the nose and inserts into the glabellar skin<sup>32,33</sup>



\*Muscles and anatomical structures shown for anatomical reference only.

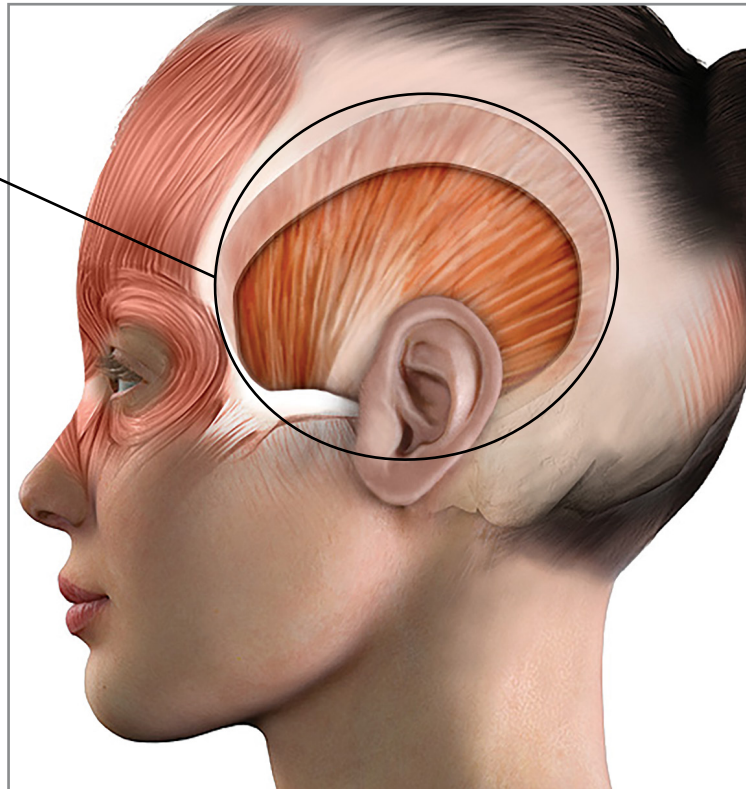
#### IMPORTANT SAFETY INFORMATION (continued) ADVERSE REACTIONS

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



### **Temporalis**

Originates from the temporal fossa and deep layer of the temporal fascia, and inserts into the top and medial surface of the coronoid process of the mandible<sup>32,33</sup>



## **Interrelationship between muscles**

- Corrugator muscle fibers and frontalis muscle fibers interdigitate in the region of the medial brow where the corrugator inserts into skin
- On the corrugator's medial aspect, it is deep to both the procerus muscle and the superficial, thinned-out frontalis muscle fibers

**Because of the close proximity of these muscles, pay close attention to the depth and angle of the needle. There can be a difference between the insertion point and where the medication is ultimately delivered.**

### **IMPORTANT SAFETY INFORMATION (continued)**

#### **ADVERSE REACTIONS (continued)**

##### **Chronic Migraine**

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), musculoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 0%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).

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 with 0.3% of placebo-treated patients.

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



## Anterior injections\* (continued)

### Functional anatomy

The **frontalis muscle** is a brow elevator, pulling the brow upward.<sup>32,33</sup> Weakening of this muscle may result in brow ptosis.

Activating the frontalis creates transverse lines on the forehead (Figure 1)<sup>32,33</sup>



Figure 1

The **corrugator muscle** is a brow depressor, pulling the brow downward.<sup>32,33</sup> Weakening of this muscle may elevate the brow.

Activating the corrugator creates vertical lines between the brow (Figure 2)<sup>32,33</sup>



Figure 2

\*Muscles and anatomical structures shown for anatomical reference only.



## Functional anatomy (continued)

The **procerus muscle** draws down the medial aspect of the brow.<sup>32,33</sup>

Activating the procerus creates a transverse ridge over the nose (Figure 3)<sup>32,33</sup>



The **temporalis** is a masticatory muscle. Clenching the teeth activates the temporalis and can help localize the muscle (Figure 4).<sup>32,33</sup>



\*This is a hypothetical patient.

## IMPORTANT SAFETY INFORMATION (continued)

### ADVERSE REACTIONS (continued)

#### Postmarketing Experience

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

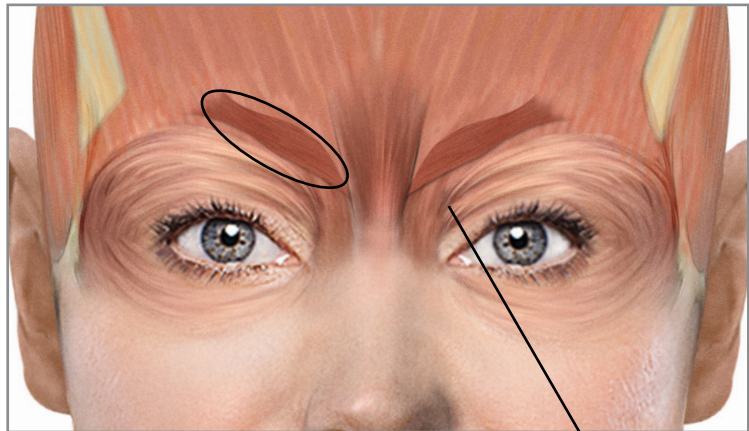
**Please see additional Important Safety Information about BOTOX® on following pages.**



## Standard corrugator PREEMPT protocol\*

### Dose<sup>5</sup>

- 5 Units (0.1 mL) in each site
- Total of 10 Units divided into 2 sites

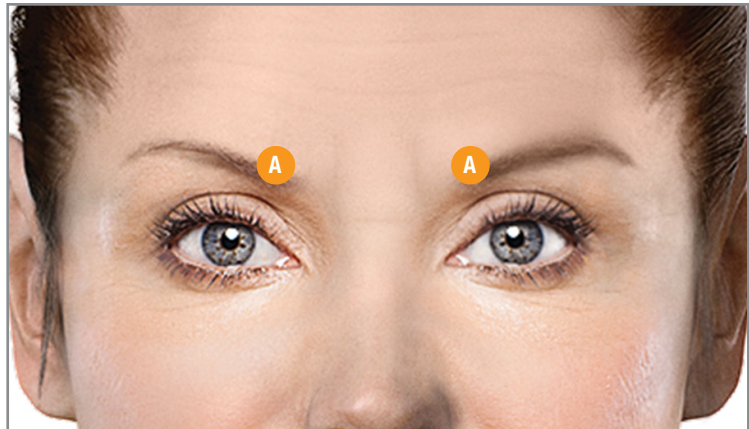


Corrugator muscle<sup>32,33,\*</sup>

Medial inferior edge of the superior orbital rim<sup>32,33,\*</sup>

### Injection site **A**

- About 1.5 cm ( $\approx$  1 fingerbreadth) above the medial inferior edge of the superior orbital rim (bony landmark). This may vary based on individual anatomy



Corrugator injection sites<sup>5</sup>

\*Muscles and anatomical structures shown for anatomical reference only.

### IMPORTANT SAFETY INFORMATION (continued) ADVERSE REACTIONS (continued)

#### Postmarketing Experience (continued)

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.



Figure 5

## Additional factors to consider prior to injection

- Ask the patient to furrow the brow, which activates the corrugator and causes medial and inferior movement of the brow
- Palpate and pinch the muscle, holding it between the thumb and index finger (Figure 5)
- Consider injecting at a 90° angle into the belly of the muscle, remaining above the periosteum, to help ensure medication delivery into the corrugator and not into a nearby muscle (Figure 5)
- Because facial anatomy is different, the standard measurements for some patients may lead to inadvertent penetration of the frontalis muscle, which may lead to brow ptosis
- Corrugator muscles are thin, so injecting too deep can hit the periosteum and may trigger headache/migraine
- Injecting with the needle pointed upward and laterally at a 45° angle may increase the risk of frontalis penetration

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

### IMPORTANT SAFETY INFORMATION (continued) DRUG INTERACTIONS

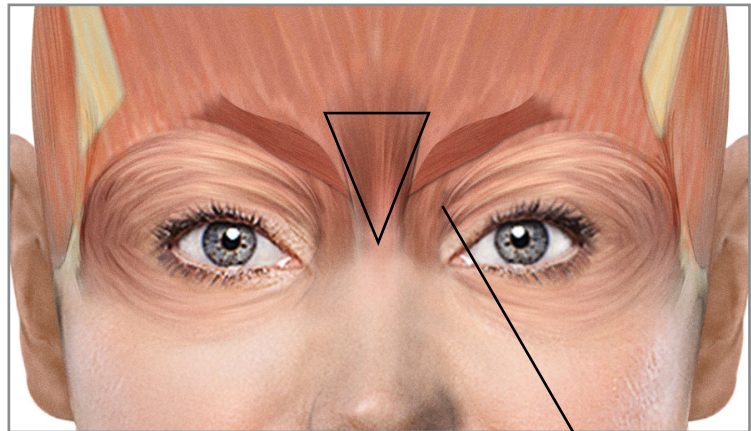
Co-administration of BOTOX® and other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic 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®.

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

## Standard procerus PREEMPT protocol\*

### Dose<sup>5</sup>

- 5 Units (0.1 mL) in 1 site
- Total of 5 Units

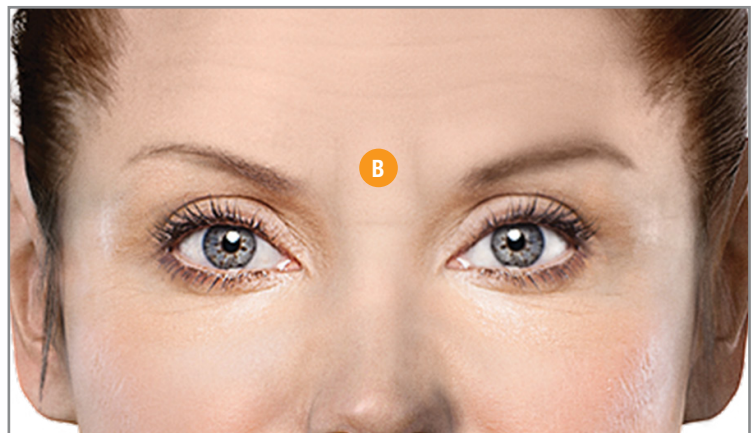


Procerus muscle<sup>32,33,\*</sup>

Medial inferior edge  
of the superior orbital rim<sup>34,\*</sup>

### Injection site **B**

- The base of the procerus resides approximately midway between the 2 corrugator injections



Procerus injection site<sup>5</sup>

\*Muscles and anatomical structures shown for anatomical reference only.

### 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 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.





### **Additional factors to consider prior to injection**

- Ask the patient to furrow the brow; use the vertical and horizontal lines as orientation sites
- Inject into the belly of the muscle at 90° to deliver medication into the procerus and not a nearby muscle (eg, frontalis) (Figure 6)
- The procerus muscle is thin, so injecting too deep can hit the periosteum
- Injecting too high in the brow area, in the lower frontalis instead of the procerus, can lead to brow ptosis

**Be mindful of the thin muscles of the forehead and brow. Stay in the most superficial aspect of the muscle to avoid hitting the periosteum.**

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

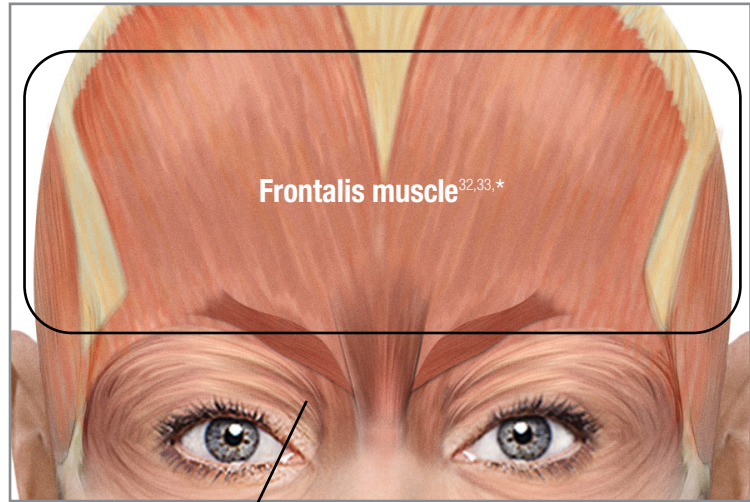
## Standard frontalis PREEMPT protocol\*

### Dose<sup>5</sup>

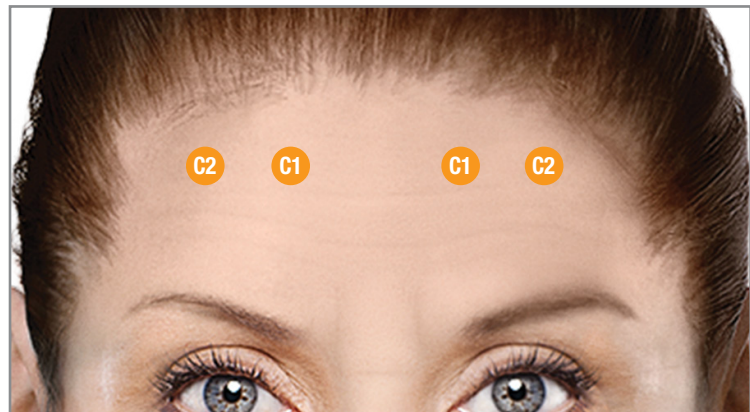
- 5 Units (0.1 mL) in each site
- Total 20 Units divided into 4 sites

### Medial injection site C1

- Visually draw a vertical line up from the medial inferior edge of the superior orbital rim
- Medial injection is generally within the upper one-third of the forehead, and at least 1.5 cm ( $\approx$  1 fingerbreadth) above the corrugator injection site. This may vary based on individual anatomy



Medial inferior edge of the superior orbital rim<sup>32,33,\*</sup>



Frontalis injection sites<sup>5</sup>

### Lateral injection site C2

- Lateral injections are parallel, lining up with the lateral limbus of the cornea, and at least 1.5 cm ( $\approx$  1 fingerbreadth) lateral to the medial injection site (Figure 7). This may vary based on individual anatomy

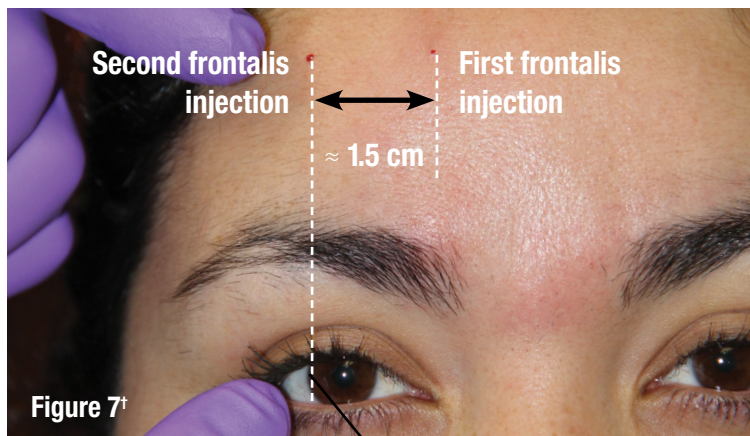


Figure 7†

Lateral limbus of the cornea<sup>34,\*</sup>

\*Muscles and anatomical structures shown for anatomical reference only.

†This is a hypothetical patient.





Figure 8

## Additional factors to consider prior to injection

- Angle the needle superiorly at 45° (Figure 8)
- Frontalis muscles are thin, so inject into the most superficial aspect of the muscle to avoid the periosteum
- Injecting in the frontalis too low may cause medial brow weakness and lateral brow elevation; the elevation occurs as a compensatory mechanism to keep the eyelids open in the presence of medial brow weakness
- Consider injecting higher (in the hairline) to avoid weakening the frontalis, which may exacerbate preexisting brow ptosis; counsel patients with this condition accordingly (see page 43)
- Consider that injection points are different than medication delivery points
- If patients are concerned about discomfort, the injector may consider a topical anesthetic in this area

**Account for individual anatomy. Forehead sizes are different, so generally stay within the upper one-third of the forehead.**

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

### **IMPORTANT SAFETY INFORMATION (continued)** **CONTRAINDICATIONS**

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

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

## Standard temporalis PREEMPT protocol\*

### Dose<sup>5</sup>

- 5 Units (0.1 mL) in each site
- Total 40 Units divided into 8 sites (4 on each side of head)

#### Injection site D1

- Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm ( $\approx$  2 fingerbreadths)

#### Injection site D2

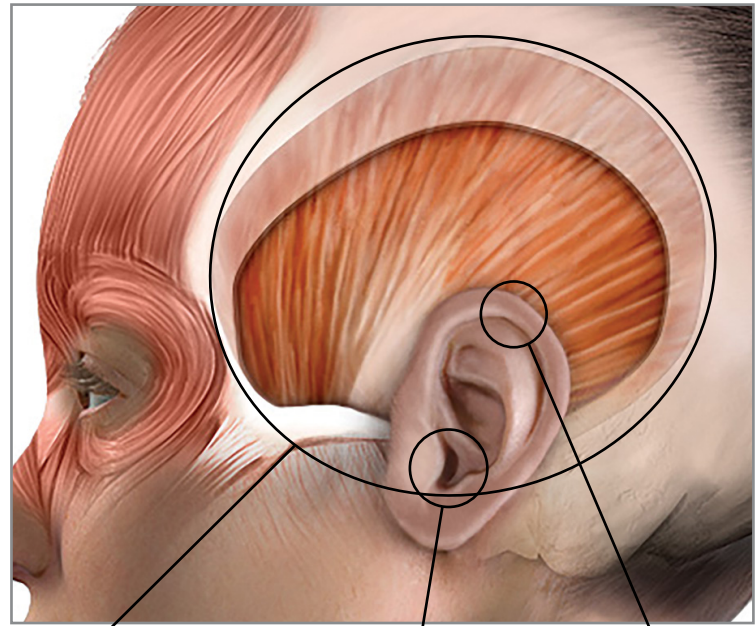
- Move about 1.5 cm to 3 cm (at least 2 fingerbreadths) up from the first injection, still in line with the tragus of the ear

#### Injection site D3

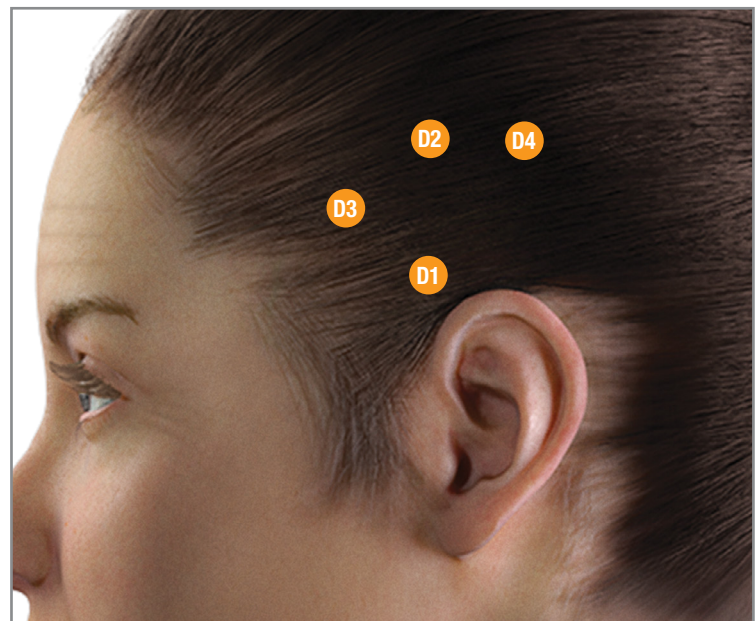
- Move about 1.5 cm ( $\approx$  1 fingerbreadth) forward, toward the face, from the first and second injections. Make the third injection halfway vertically between injection sites 1 and 2

#### Injection site D4

- Move about 1.5 cm ( $\approx$  1 fingerbreadth) back from the second injection, and in line with the midportion (helix) of the ear



Temporalis muscle<sup>32,33,\*</sup> Tragus of the ear<sup>32,33,\*</sup> Superior helix<sup>35,\*</sup>



Temporalis injection sites<sup>5</sup>

\*Muscles and anatomical structures shown for anatomical reference only.





Figure 9

## Additional factors to consider prior to injection

- Inject the most superficial aspect of the muscle at 45° (Figure 9)
- Aspirate to ensure no blood return
- Keep injections within the hairline, particularly for the most anterior injection site; the needle should be angled posteriorly (Figure 9)
- Clenching the teeth activates the temporalis and can help localize the muscle
- Area may be prone to bleeding. Apply pressure immediately and manage before the patient leaves
- A finger can be placed on the middle of the helix of the ear to guide the fourth injection
- The temporalis is covered by a thick fascia made up of fibrous bands, and patients may hear the injection needle passing through this fascia

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

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

#### 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 dose have been reported.

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

## Posterior injections\*

### Muscles of the neck and posterior head

#### **Occipitalis**

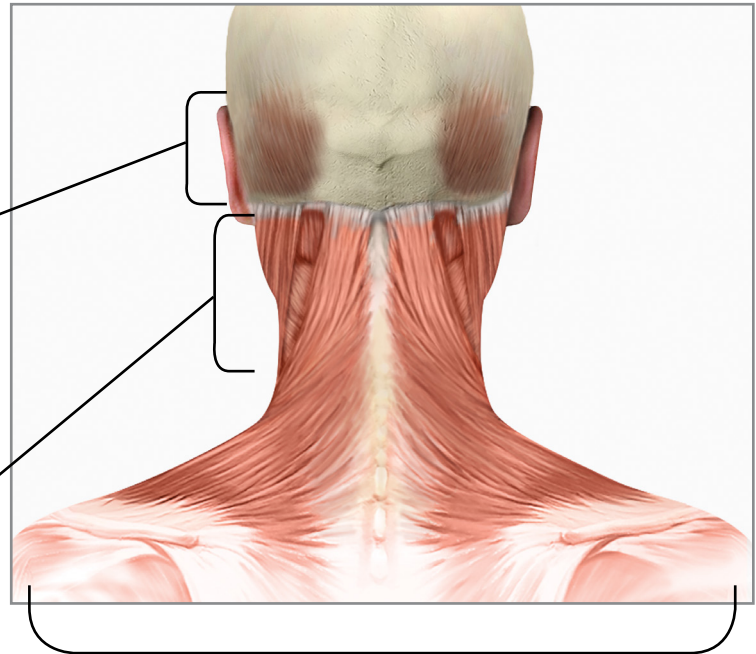
Originates at the highest nuchal line and inserts into the epicranial aponeurosis, which is attached to the frontalis<sup>32,33</sup>

#### **Cervical paraspinal muscles**

Should be considered a group (including the splenius capitis and semispinalis capitis) running deep alongside the cervical spine<sup>32,33</sup>

#### **Trapezius**

A flat, triangular muscle situated over the back of the neck and upper thorax<sup>32,33</sup>



\*Muscles and anatomical structures shown for anatomical reference only.

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

#### **Lack of Interchangeability Between Botulinum Toxin Products**

The potency Units of BOTOX<sup>®</sup> 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<sup>®</sup> cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

#### **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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. The safety and effectiveness of BOTOX<sup>®</sup> for unapproved uses have not been established.



## Functional anatomy



Figure 10

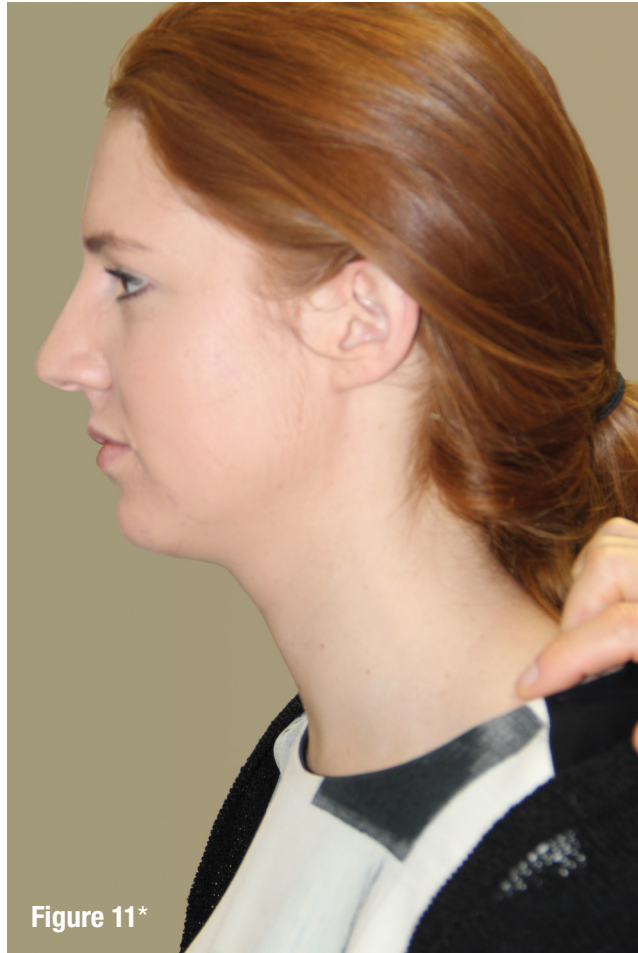


Figure 11\*

One function of the **occipitalis** is as an anchor for the frontalis.<sup>32,33</sup>

**Cervical paraspinal muscles** stabilize and allow for movement of the head and cervical spine (Figure 10).<sup>32,33</sup>

In addition to the muscles that are deep to the trapezius, the **trapezius** functions to stabilize and bend the head and neck backward and laterally (Figure 11).<sup>32,33</sup>

\*This is a hypothetical patient.

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

#### Hypersensitivity Reactions

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

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



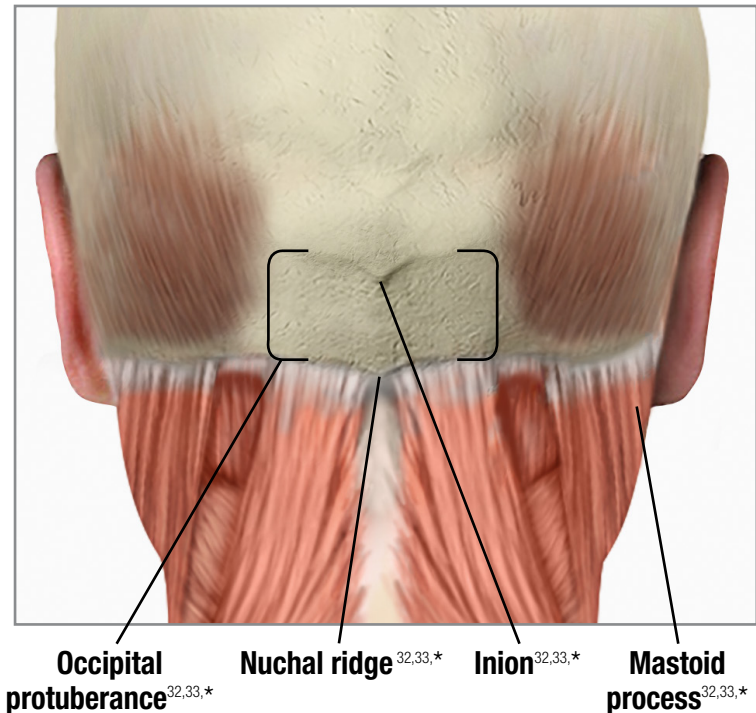
## Standard occipitalis PREEMPT protocol\*

### Dose<sup>5</sup>

- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

#### Injection site **E1**

- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 12)
- Locate the tip of the mastoid process behind the ear (Figure 12)
- Place your thumb on the midpoint of the occipital protuberance (inion) and your index finger on tip of the mastoid process
- Divide the space between your thumb and index finger in half
- Place the first injection just above the nuchal ridge at this midpoint

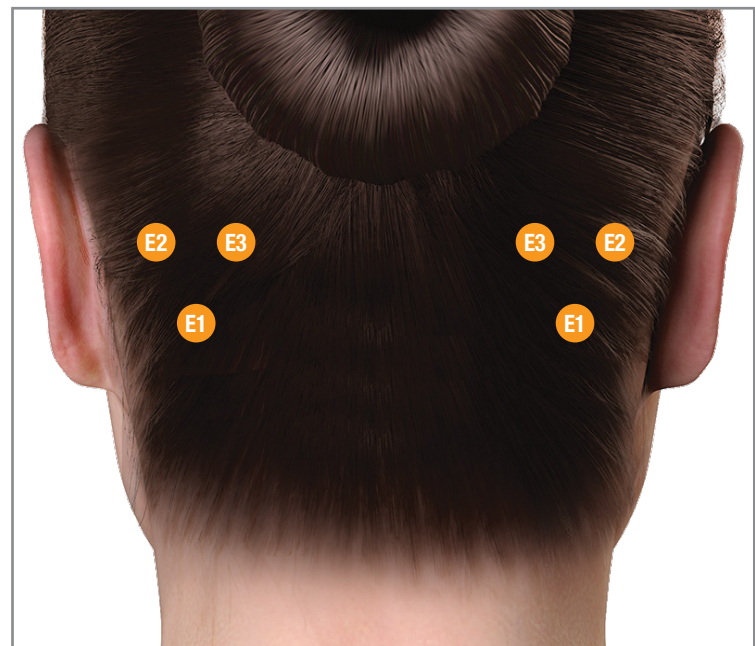


#### Injection site **E2**

- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 32) for the second muscle area for injection (ie, at the 10 o'clock position for the left injection)

#### Injection site **E3**

- Measure a diagonal fingerbreadth up and medial for the third muscle area for injection (ie, at the 2 o'clock position for the left injection)



**Occipitalis injection sites<sup>5</sup>**

\*Muscles and anatomical structures shown for anatomical reference only.



Figure 12\*



Figure 13

## Additional factors to consider prior to injection

- The occipitalis muscle is shallow
- Inject the most superficial aspect of the muscle, which will be just upon penetration of the dermis (Figure 13)
- Inject at 45°, angling the needle upward and away from the neck (Figure 13)
- Injecting too low in the neck may result in neck pain and weakness; inject above the nuchal ridge

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

\*This is a hypothetical patient.

### **IMPORTANT SAFETY INFORMATION (continued)**

#### **WARNINGS AND PRECAUTIONS (continued)**

##### **Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders**

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin.

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



## Standard cervical paraspinal PREEMPT protocol\*

### Dose<sup>5</sup>

- 5 Units (0.1 mL) in each site
- Total 20 Units divided into 4 sites (2 on each side)

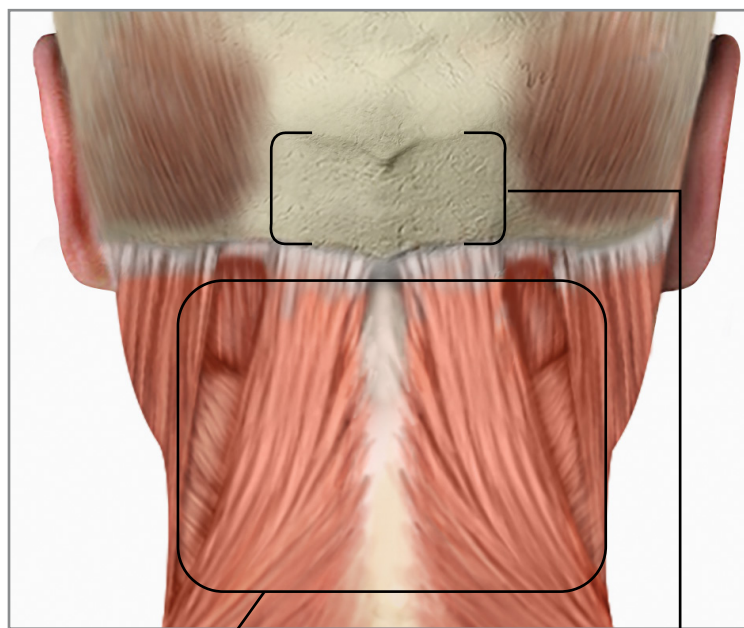
### Injection site F1

- Measure about 1 cm left of the midline of the cervical spine and about 3 cm ( $\approx$  2 fingerbreadths) inferior to the lower border of the occipital protuberance

### Injection site F2

- Measure about 1.5 cm ( $\approx$  1 fingerbreadth) diagonally up at a 45° angle toward the helix of the ear (see diagram on page 32) from the first injection site

\*Muscles and anatomical structures shown for anatomical reference only.



Cervical paraspinal muscle group<sup>32,33,\*</sup> Occipital protuberance<sup>32,33,\*</sup>



Cervical paraspinal injection sites<sup>5</sup>

### IMPORTANT SAFETY INFORMATION (continued)

#### WARNINGS AND PRECAUTIONS (continued)

#### Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders (continued)

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*).



Figure 14

## Additional factors to consider prior to injection

- Assess patient for preexisting neck pain/weakness to help properly set expectations about this muscle group
- Position the patient upright, with the head in a neutral position; flexing too far forward may result in injecting too deep
- Visualize a line across the neck,  $\approx$  2 fingerbreadths down from the occipital protuberance, and avoid injecting below the line (Figure 14)
- Inject higher (in the hairline) to help minimize the potential for neck weakness—consider this area the suboccipitalis region
- Inject into the most superficial aspect of the muscle, angling  $45^\circ$  and superiorly
- Penetrating the fascia should be sufficient to avoid injecting too deep
- Cervical paraspinal muscles are a group of muscles running deep to the cervical spine (see posterior anatomy on page 34 for details)

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

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

#### Dysphagia and Breathing Difficulties

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

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

## Standard trapezius PREEMPT protocol\*

### Dose<sup>5</sup>

- 5 Units (0.1 mL) in each site
- Total 30 Units divided into 6 sites (3 on each side)

#### Injection site **G1**

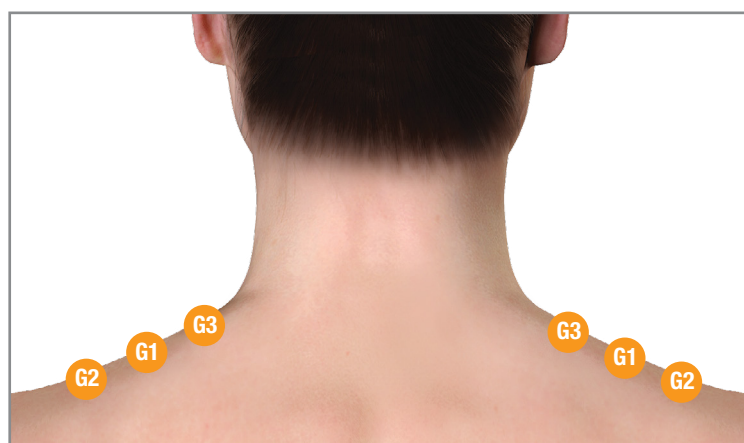
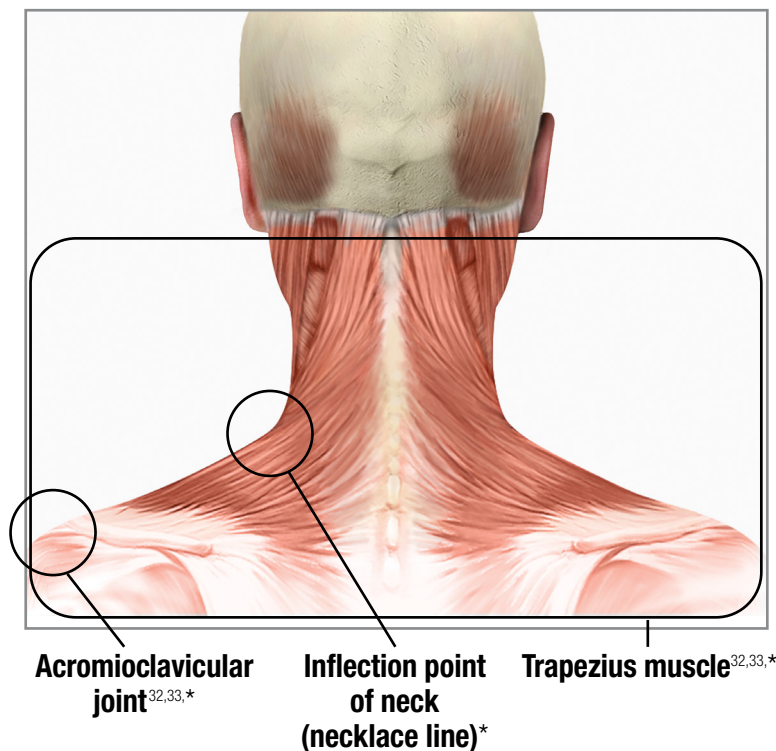
- Divide the upper portion of the trapezius muscle in half, from the inflection point of the neck (necklace line) to the acromioclavicular joint
- The first injection is located at this midpoint

#### Injection site **G2**

- Split the difference between injection 1 and the acromioclavicular joint

#### Injection site **G3**

- Split the difference between injection 1 and the necklace line



**Trapezius injection sites<sup>5</sup>**

\*Muscles and anatomical structures shown for anatomical reference only.

### IMPORTANT SAFETY INFORMATION (continued)

#### WARNINGS AND PRECAUTIONS (continued)

##### Human Albumin and Transmission of Viral Diseases

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





Figure 15

## Additional factors to consider prior to injection

- Assess patient for possible preexisting neck/shoulder weakness to help properly set expectations about injecting this muscle
- Inject horizontal to the muscle to avoid injecting too deep (Figure 15)
- Inject the supraclavicular portion of the muscle, lateral to the neckline and medial to the deltoid/acromioclavicular joint (Figure 15)
- Injecting too high into the cervical spine area or too deep may lead to neck weakness, pain, and compensatory muscle activity
- Patients with small frames may be predisposed to weakness in this area

Note: The considerations above cannot eliminate the risk of adverse events following BOTOX® injections.

### IMPORTANT SAFETY INFORMATION (continued) ADVERSE REACTIONS

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

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

## Patient assessment before injection\*

Before any injections occur, patients should be evaluated for conditions that may be affected or exacerbated by treatment. If any conditions are found to exist, the injector should inform and counsel the patient. Proper counseling will help set patient expectations. Patients with preexisting conditions should be carefully assessed to determine if they're appropriate for injection.

### PATIENT EXAMINATION:

- ✓ Visually **inspect** the muscle
- ✓ Ask the patient to **activate** the muscle
- ✓ **Palpate** the muscle

### Pre-examination of the brow

**What to look for:** Inspect for excessive soft tissue resting near the upper lid of the eye and lid drooping (Figure 16).

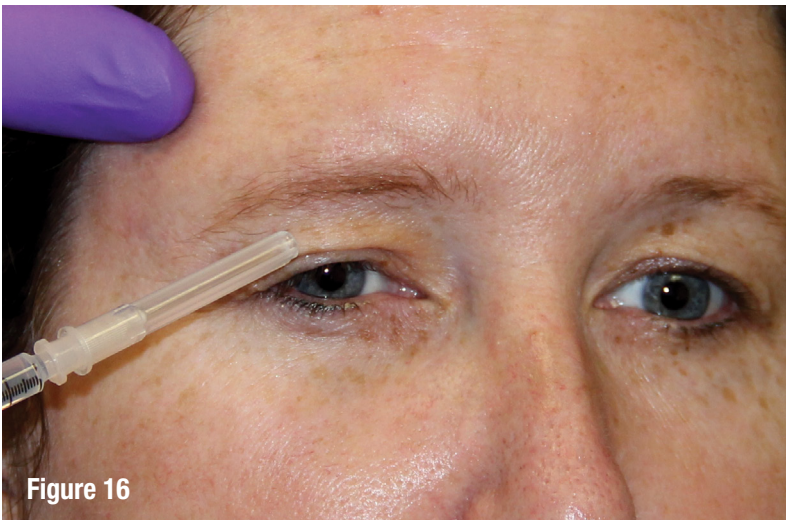


Figure 16

\*Muscles and anatomical structures shown for anatomical reference only.

**DIALOGUE TIP:** “**BOTOX**<sup>®</sup> is locally administered, with **purposeful injections** across 7 head/neck muscle areas that may be associated with migraine (31 injections).”<sup>5</sup>

### IMPORTANT SAFETY INFORMATION (continued) ADVERSE REACTIONS (continued)

#### Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX<sup>®</sup> for Chronic Migraine vs placebo include, respectively: neck pain (9% vs 3%), headache (5% vs 3%), eyelid ptosis (4% vs < 1%), migraine (4% vs 3%), muscular weakness (4% vs < 1%), musculoskeletal stiffness (4% vs 1%), bronchitis (3% vs 2%), injection-site pain (3% vs 2%), musculoskeletal pain (3% vs 1%), myalgia (3% vs 1%), facial paresis (2% vs 0%), hypertension (2% vs 1%), and muscle spasms (2% vs 1%).



## Pre-examination of the brow (continued)

Ptosis may be a preexisting condition or may occur after BOTOX® treatment. Patients should be evaluated for both eyelid and eyebrow ptosis.



### Lid ptosis

Notice the asymmetry as a result of the drooping lid.<sup>32,\*</sup>



### Medial brow ptosis

Notice the medial brow depression and lateral brow elevation.\*



### Pseudoptosis

Notice the extra soft tissue around the eyelid and the misalignment of the lids.<sup>32,\*</sup>



### Full brow ptosis

Notice how the weakened frontalis muscle has depressed both the medial and lateral brow.\*

## Pre-examination of the forehead

**What to look for:** Brow ptosis, possibly compensated by active frontalis muscles, of which the patient may be unaware.

**How to examine:** Ask the patient to activate the frontalis muscle by raising and lowering the eyebrows (Figure 21). Observe the dynamic muscle activity and whether there is any compensatory mechanism keeping the eyelids open in the presence of brow weakness.



\*Muscles and anatomical structures shown for anatomical reference only.

† This is a hypothetical patient.

## IMPORTANT SAFETY INFORMATION (continued)

### ADVERSE REACTIONS (continued)

#### Chronic Migraine (continued)

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 with 0.3% of placebo-treated patients.

#### Postmarketing Experience

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

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



## Patient assessment before injection (continued)\*

### Pre-examination of the neck

**What to look for:** Neck pain and neck weakness may be present among Chronic Migraine patients.<sup>32</sup> Inspect the patient for a head-forward position, which may indicate preexisting muscle weakness (Figure 22).



Figure 22<sup>†</sup>

**Three-fingerbreadths, head-forward position**

**DIALOGUE TIP:** “**BOTOX**<sup>®</sup> is given with **tiny needles**, which are about the thickness of 5 human hairs. The shallow injections may feel like tiny **pinches or pinpricks**.”

\*Muscles and anatomical structures shown for anatomical reference only.

<sup>†</sup>This is a hypothetical patient.

### **IMPORTANT SAFETY INFORMATION (continued)** **ADVERSE REACTIONS (continued)**

#### **Postmarketing Experience (continued)**

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.

**How to examine:** Observe the patient, standing, in profile with a neutral-spine position. Look for a plumb (vertical) line from the tragus and anterior ridge of the trapezius through the patient's center of gravity (Figure 23). If the tragus is anterior to this line by 2 to 3 fingerbreadths, this may be abnormal (Figure 22).

**Prior to BOTOX® injections, consider pre-examining patients for pain sensitivity in the neck.**

**Figure 23\***

\*This is a hypothetical patient.

**IMPORTANT SAFETY INFORMATION (continued)**  
**DRUG INTERACTIONS**

Co-administration of BOTOX® and 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®.

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

# A comprehensive Chronic Migraine management plan may be needed

## Considerations for a multidisciplinary approach in Chronic Migraine<sup>7,8,36-38</sup>:

### MANAGE MEDICATIONS

- Review medical history to determine which treatments the patient has tried in the past
- Ensure adequate prevention
  - Determine if patient is retrying a preventive treatment at a different dose
- Assess acute medication use

### ADDRESS COMORBIDITIES

- |                       |                       |                |
|-----------------------|-----------------------|----------------|
| • Allergies/hay fever | • High cholesterol    | • Chronic pain |
| • Sinusitis           | • High blood pressure | • Anxiety      |
| • Depression          | • Arthritis           | • Obesity      |



## ADJUST LIFESTYLES

- Maintain a healthy diet
- Exercise regularly
- Limit caffeine
- Manage stress
- Attain a regular sleep pattern

## CHANGE BEHAVIORS

- Biofeedback therapy
- Cognitive therapy

### 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 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.



# Tips to help efficiently administer BOTOX<sup>®</sup> treatment in the office

## Office staff and processes:

- **Assign staff to specific roles**

- ☒ Roles include ordering BOTOX<sup>®</sup> and submitting insurance verifications, prior authorizations, and claims

- **Have a process to identify Chronic Migraine patients**

- ☒ Use a headache diary, screener, intake form, and/or symptom assessment tool to document symptoms and medication history

- **Use a system to track and schedule recurring BOTOX<sup>®</sup> treatment**

- ☒ Ensure patients receive treatment every 12 weeks
- ☒ Send reminders 1 to 2 weeks before the appointment

- **Set up BOTOX<sup>®</sup> Clinic Days from the beginning**

- ☒ May improve patient access and the efficiency of paperwork processing by having a dedicated time and place for procedures

- **Consider involving additional office staff to help**

- ☒ Include NPs/PAs for follow-ups, patient counseling, and injections, as appropriate
- ☒ Train nursing staff to reconstitute and prepare syringes for BOTOX<sup>®</sup> treatment

## **IMPORTANT SAFETY INFORMATION (continued)**

### **CONTRAINDICATIONS**

BOTOX<sup>®</sup> is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

### **WARNINGS AND PRECAUTIONS**

#### **Spread of Toxin Effect**

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX<sup>®</sup> for Chronic Migraine at the labeled dose have been reported.

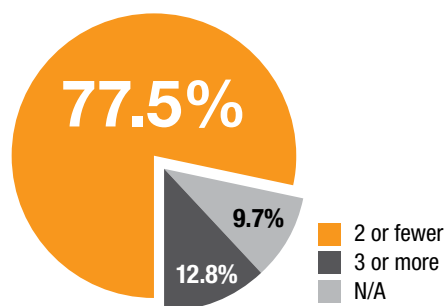
# Your patients may meet their insurance policy requirements for BOTOX® treatment

Nearly all insurance plans cover BOTOX® for Chronic Migraine<sup>39,40</sup>

**98%** of commercial lives covered

**100%** of Medicare lives covered\*

Majority of lives require trial of 2 or fewer oral preventives<sup>41,†</sup>



Based on data covering 244,831,608 medical lives.

Chronic Migraine patients have tried

**4.7**

preventive treatments on average (n = 280)<sup>42</sup>

## Insurance documentation requirements

Consult individual policies for specific requirements for BOTOX®. Generally, you may need the following for insurance purposes:

- Medication history
  - Number of oral preventives needed
  - Types of therapeutic classes
  - Required duration of each treatment trial (if any)
  - Whether medications with contraindications or intolerance concerns may count as a treatment trial
- Defined medical necessity
- Services provided
- BOTOX® administration details (sites, Units, schedule)
- Clinical effectiveness and/or outcomes of BOTOX® therapy

\*Not a guarantee of coverage, or partial or full payment. Check each patient's coverage with applicable insurer. Formulary coverage does not imply safety or efficacy.

†As of Q2 2015.

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

#### 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.

# Resources available to help your patients access BOTOX®



## Samples

- Available for same-day treatment so appropriate new Chronic Migraine patients can evaluate efficacy and safety
- **Talk to your Allergan® sales representative to learn more**



## Savings

- The average out-of-pocket cost per treatment before the BOTOX® Savings program is \$187<sup>43</sup>
- Eligible, commercially insured patients may pay as little as \$0 for BOTOX® treatments\*
- Costs of both the product and procedure may be covered
- Maximum savings limit of \$1000 per treatment for up to 4 treatments over a 12-month period
- **Recommend that your patients check their eligibility for the BOTOX® Savings Program at their first appointment**



## Support

- Allergan® provides resources and in-office insights that help streamline BOTOX® office processes, including:
  - Seeking reimbursement
  - Prior authorization
  - Product acquisition
  - Retreatment
- **Talk to your Allergan® sales representative to learn more**

\*Restrictions and maximum savings limits apply. Patient out-of-pocket expense may vary. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs. Please see full terms and conditions herein and at [BOTOXSavingsProgram.com](http://BOTOXSavingsProgram.com). For questions about this program, please call 1-800-44-BOTOX.

### BOTOX® Savings Program Terms and Conditions

**Program Terms, Conditions, and Eligibility Criteria:** **1.** This offer is good for use only with a valid prescription for BOTOX® (onabotulinumtoxinA). **2.** Based on insurance coverage, each patient can be reimbursed up to \$1000 per treatment with a maximum savings limit of \$4000 per year. Patient out-of-pocket expense may vary. **3.** This offer is not valid for use by patients enrolled in Medicare, Medicaid, or other federal or state programs (including any state pharmaceutical assistance programs), or private indemnity or HMO insurance plans that reimburse you for the entire cost of your prescription drugs. Patients may not use this offer if they are Medicare-eligible and enrolled in an employer-sponsored health plan or prescription drug benefit program for retirees. This offer is not valid for cash-paying patients. **4.** This offer is valid for up to 4 treatments over a 12-month period. **5.** Offer is valid only for BOTOX® and BOTOX® treatment-related costs not covered by insurance. **6.** A BOTOX® Savings Program check will be provided upon approval of a claim. The claim must be submitted with treatment details from an Explanation of Benefits (EOB) or a Specialty Pharmacy (SP) receipt. (If the BOTOX® prescription was filled by a Specialty Pharmacy, both EOB and SP details must be provided.) All claims must be submitted within 120 days of treatment date. You may be required to provide a copy of your EOB or SP receipt for your claim to be approved. **7.** A BOTOX® Savings Program check may be sent either directly to you or to your selected healthcare provider who provided treatment. For payment to be made directly to your healthcare provider, you must authorize an assignment of benefit during each claim submission. You are not obligated to assign your BOTOX® Savings Program benefit to your healthcare provider to participate in the program. **8.** Allergan® reserves the right to rescind, revoke, or amend this offer without notice. **9.** Offer good only in the USA, including Puerto Rico, at participating retail locations. **10.** Void where prohibited by law, taxed, or restricted. **11.** This offer is not health insurance. **12. By participating in the BOTOX® Savings Program, you acknowledge that you are an eligible patient and that you understand and agree to comply with the terms and conditions of this offer.**

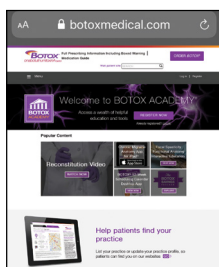
For questions about this program, please call 1-800-44-BOTOX.

# Resources available to help patients, clinicians, and office staff



## Patient brochures

- Brochures are available for both current and prospective patients to help them understand what to expect with BOTOX® treatment (also available in Spanish)
- **Ask your Allergan® sales representative or visit [BOTOXMedical.com](http://BOTOXMedical.com) for this brochure**



## BOTOX Academy®

- Videos and e-lectures on:
  - Injection technique
  - Muscle localization
  - Functional anatomy
  - Reconstitution
- Downloadable patient education and office materials
- **Register at [BOTOXAcademy.com](http://BOTOXAcademy.com)**



## Peer-to-peer training

- Preceptorships, Proctorships, Expert-On-Demand programs (teleconference with a Chronic Migraine expert), Local Live/dinner programs, and Advanced Case-Based Discussions workshops are available to help improve your injection technique
- **Ask your Allergan® sales representative or visit [BOTOXAcademy.com](http://BOTOXAcademy.com) to learn more**

**DIALOGUE TIP:** “If you’re eligible, the BOTOX® Savings Program may make treatment affordable for you. I recommend visiting [BOTOXSavingsProgram.com](http://BOTOXSavingsProgram.com) to learn more and get started.”

## 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, including Boxed Warning, about BOTOX® throughout this brochure.**

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[illegible]



## Reconstitution pocket guide

**BOTOX**  
onabotulinumtoxinA injection



### Reconstitution/Injection Pocket Card

This pocket card is a reference guide for BOTOX® (onabotulinumtoxinA) injection sites for Chronic Migraine patients. The reconstitution materials, dilution table, and Injection Paradigm are highlighted for quick reference.

#### Indication Chronic Migraine

BOTOX® for injection 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).

#### Limitations of Use

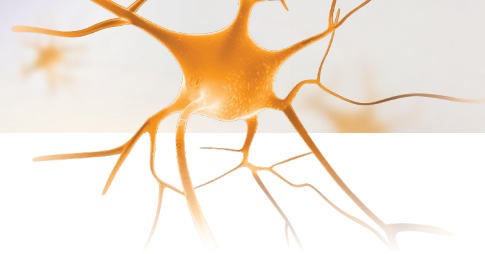
Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

#### 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 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® inside.



# Helpful phone numbers and websites

## ORDERING

AllerganDirect.com or call 1-800-44-BOTOX (1-800-442-6869)

## CUSTOMER SERVICE

1-800-44-BOTOX (1-800-442-6869)

## ALLERGAN® MEDICAL INFORMATION LINE

1-800-433-8871

## PATIENT FINANCIAL ASSISTANCE

For commercially insured patients: BOTOXSavingsProgram.com

## PROFESSIONAL EDUCATION & RESOURCES

For injection training opportunities: Contact your Allergan® sales representative

For Reimbursement Business Advisors: Contact your Allergan® sales representative

For injection and reconstitution videos, plus downloadable patient education and more: BOTOXAcademy.com

Please see BOTOX® full [Prescribing Information](#), including [Boxed Warning](#) and [Medication Guide](#).

**References:** 1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. 2. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1211-1259. 3. World Health Organization. Global burden of disease 2004. Part 3. Disease incidence, prevalence and disability. [http://who.int/healthinfo/global\\_burden\\_disease/GBD\\_report\\_2004update\\_part3.pdf](http://who.int/healthinfo/global_burden_disease/GBD_report_2004update_part3.pdf). Published March 2004. Accessed March 3, 2020. 4. Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. *Headache*. 2011;51(suppl 2):77S-83S. 5. BOTOX® Prescribing Information, October 2019. 6. American Migraine Foundation. The timeline of a migraine attack. <https://americanmigrainefoundation.org/understanding-migraine/timeline-migraine-attack>. Accessed March 3, 2020. 7. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia*. 2011;31(3):301-315. 8. Buse DC, Manack A, Serrano D, Turkel C, Lipton RB. Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. *J Neurol Neurosurg Psychiatry*. 2010;81(4):428-432. 9. Aurora SK, Brin MF. Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. *Headache*. 2017;57(1):109-125. 10. Bigal ME, Lipton RB. Concepts and mechanisms of migraine chronification. *Headache*. 2008;48(1):7-15. 11. Buse DC, Greisman JD, Baiji K, Lipton RB. Migraine progression: a systematic review. *Headache*. 2019;59(3):306-338. 12. Ashina S, Serrano D, Lipton RB, et al. Depression and risk of transformation of episodic to chronic migraine. *J Headache Pain*. 2012;13(8):615-624. 13. Schwedt TJ, Chong CD, Wu T, Gaw N, Fu Y, Li J. Accurate classification of chronic migraine via brain magnetic resonance imaging. *Headache*. 2015;55(6):762-777. 14. Lipton RB, Cady RK, Stewart WF, Wilks K, Hall C. Diagnostic lessons from the spectrum study. *Neurology*. 2002;58(9)(suppl 6):27S-31S. 15. Drossman DA. 2012 David Sun lecture: Helping your patient by helping yourself—how to improve the patient-physician relationship by optimizing communication skills. *Am J Gastroenterol*. 2013;108(4):521-528. 16. Data on file, Allergan; PREEMPT 1 Final Report. 17. Data on file, Allergan; PREEMPT 2 Final Report. 18. Data on file, Allergan; PREEMPT 1 Efficacy Data. 19. Data on file, Allergan; PREEMPT 2 Efficacy Data. 20. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack Adams A. Long-term study of the efficacy and safety of onabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. *J Headache Pain*. 2018;19(1):1-12. 21. Winner PK, Blumenfeld AM, Eross EJ, et al. Long-term safety and tolerability of onabotulinumtoxinA treatment in patients with chronic migraine: results of the COMPEL study. *Drug Saf*. 2019;42(8):1013-1024. 22. Data on file, Allergan; COMPEL Data. 23. Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache*. 2010;50(9):1406-1418. 24. Dodick DW, Turkel CC, DeGryse RE, et al; PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;50(6):921-936. 25. Binder WJ, Brin MF, Blitzer A, Schoenrock LD, Pogoda JM. Botulinum toxin type A (BOTOX®) for treatment of migraine headaches: an open-label study. *Otolaryngol Head Neck Surg*. 2000;123(6):669-676. 26. Elkind AH, O'Carroll P, Blumenfeld A, DeGryse R, Dimitrova R; for the BoNTA-024-026-036 Study Group. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. *J Pain*. 2006;7(10):688-696. 27. Saper JR, Mathew NT, Loder EW, DeGryse R, VanDenburgh AM; for the BoNTA-009 Study Group. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type A injection sites and doses in the prevention of episodic migraine. *Pain Med*. 2007;8(6):478-485. 28. Relja M, Poole AC, Schoenen J, Pascual J, Lei X, Thompson C; for the European BoNTA Headache Study Group. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia*. 2007;27(6):492-503. 29. Aurora SK, Gawel M, Brandes JL, Pokta S, VanDenburgh AM; BOTOX® North American Episodic Migraine Study Group. Botulinum toxin type A prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. *Headache*. 2007;47(4):486-499. 30. Silberstein SD, Stark SR, Lucas SM, Christie SN, DeGryse RE, Turkel CC; BoNTA-039 Study Group. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clin Proc*. 2005;80(9):1126-1137. 31. Mathew NT, Frisberg BM, Gawel M, Dimitrova R, Gibson J, Turkel C; BOTOX® CDH Study Group. Botulinum toxin type A (BOTOX®) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Headache*. 2005;45(4):293-307. 32. Blumenfeld AM, Silberstein SD, Dodick DW, Aurora SK, Brin MF, Binder WJ. Insights into the functional anatomy behind the PREEMPT injection paradigm: guidance on achieving optimal outcomes. *Headache*. 2017;57(5):766-777. 33. Standring S, ed. *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. 40th ed. London, England: Churchill Livingstone; 2008. 34. Miloro M, Ghali GE, Larsen P, Waite P. *Peterson's Principles of Oral and Maxillofacial Surgery*. 3rd ed. Shelton, CT: People's Medical Publishing-USA; 2011. 35. *Stedman's Medical Dictionary*. 28th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006. 36. Dodick DW. Chronic daily headache. *N Engl J Med*. 2006;354(2):158-165. 37. Silberstein SD; US Headache Consortium. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762. 38. Buse DC, Andrasik F. Behavioral medicine for migraine. *Neurol Clin*. 2009;27(2):445-465. 39. Data on file, Allergan, November 15, 2019; BOTOX® Therapeutic Payer Coverage. 40. Data on file, Allergan, November 19, 2019; BOTOX® Chronic Migraine Medicare Coverage. 41. Data on file, Allergan; Preventives Policy Analysis. 42. Data on file, Allergan, June 2018; BOTOX® Chronic Migraine Patient ATU Study Final Report. 43. Data on file, Allergan, October 2019; BOTOX® Out-of-Pocket Cost Analysis.

The following supplies will be needed prior to beginning the reconstitution procedure:



- One 200-Unit vial of BOTOX® (onabotulinumtoxinA)
- One 21-gauge, 2-inch needle (for reconstitution)
- One 5-mL syringe
- Four 1-mL tuberculin syringes (for injection)
- At least four 30-gauge, 0.5-inch needles (for injection)
- One 10-mL single-use vial of preservative-free, 0.9% sodium chloride (saline)
- Alcohol swabs for cleaning the rubber stoppers on the saline and BOTOX® vials
- Gauze pads
- 1 pair of gloves
- Hazardous medical waste container

Ensure you have received authentic BOTOX® from Allergan®. Look for the holographic film on the vial; “Allergan®” should appear within the rainbow lines.



**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.

**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 (eg, 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*).

**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*).

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

**IMPORTANT SAFETY INFORMATION (continued)**  
**ADVERSE REACTIONS**  
Adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

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

**Postmarketing Experience**  
Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

**DRUG INTERACTIONS**  
Co-administration of BOTOX® and 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 accompanying full Prescribing Information, including Boxed Warning and Medication Guide.**

**References:** 1. Blumenfeld A, Silberstein SD, Dodick DW, Aurora SK, Turkel CC, Binder WJ. Method of injection of onabotulinumtoxinA for chronic migraine: a safe, well-tolerated, and effective treatment paradigm based on the PREEMPT clinical program. *Headache*. 2010;50(9):1406-1418. 2. BOTOX® Prescribing Information, October 2019.



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BOTOXMedical.com/ChronicMigraine 1-800-44-BOTOX



# Reconstitution/Injection Pocket Card

This pocket card is a reference guide for BOTOX® (onabotulinumtoxinA) injection sites for Chronic Migraine patients. The reconstitution materials, dilution table, and Injection Paradigm are highlighted for quick reference.

**Indication**  
**Chronic Migraine**

BOTOX® for injection 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).

**Limitations of Use**  
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.

**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 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® inside.





# BOTOX® Injection Sites and Order of Injection

0.1 mL (5 Units) of BOTOX® per site<sup>1,2,\*</sup>

|               | Dilution   |   |
|---------------|--|---|
|               | Saline added<br>(0.9% sodium chloride injection) | Resulting BOTOX® dose<br>(Units per 0.1 mL) |
| 100-Unit Vial | 2 mL   | 5 Units                                     |
| 200-Unit Vial | 4 mL   | 5 Units                                     |

Resulting concentration is 5 Units per 0.1 mL.

- Upon completion of reconstitution, you will have 4 tuberculin syringes, each with 1 mL of BOTOX® and a 30-gauge, 0.5-inch needle attached

| Order      | Muscle                            | Total Recommended Dosage <sup>a</sup> |
|------------|-----------------------------------|---------------------------------------|
| A          | Corrugator <sup>b</sup>           | 10 Units divided in 2 sites           |
| B          | Procerus                          | 5 Units in 1 site                     |
| C          | Frontalis <sup>b</sup>            | 20 Units divided in 4 sites           |
| D          | Temporalis <sup>b</sup>           | 40 Units divided in 8 sites           |
| E          | Occipitalis <sup>b</sup>          | 30 Units divided in 6 sites           |
| F          | Cervical paraspinals <sup>b</sup> | 20 Units divided in 4 sites           |
| G          | Trapezius <sup>b</sup>            | 30 Units divided in 6 sites           |
| Total Dose |                                   | 155 Units divided in 31 sites         |

<sup>a</sup>Each intramuscular (IM) injection site = 0.1 mL = 5 Units of BOTOX®.

<sup>b</sup>Dose distributed bilaterally.

**A. Corrugator**  
10 Units divided in 2 sites



**B. Procerus**  
5 Units in 1 site



**C. Frontalis**  
20 Units divided in 4 sites



**D. Temporalis**  
40 Units divided in 8 sites



**E. Occipitalis**  
30 Units divided in 6 sites



**F. Cervical paraspinals**  
20 Units divided in 4 sites



**G. Trapezius**  
30 Units divided in 6 sites

The dosing and administration of BOTOX® is a detailed process. The information on this page contains highlights only and is not meant to be a substitute for appropriate training or review of full Prescribing Information.

\*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 Sections 2.1 and 2.2 of the full Prescribing Information for preparation and dilution techniques and additional dosing information).

**IMPORTANT SAFETY INFORMATION (continued)**

**CONTRAINDICATIONS**  
BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

**WARNINGS AND PRECAUTIONS**

**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 dose have been reported.

**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 reverse side.

## 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. (5.1)

### RECENT MAJOR CHANGES

|   |         |
|---|---------|
| Indications and Usage, Spasticity (1.3)   | 7/2020  |
| Dosage and Administration, Instructions for Safe Use (2.1)  | 10/2019 |
| Dosage and Administration, Pediatric Spasticity (2.6)   | 7/2020  |
| Warnings and Precautions, Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity (5.10) | 10/2019 |

### 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 patients 2 years of age and older (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 and older (1.6)
- Treatment of strabismus in patients 12 years of age and older (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 hyperhidrosis in body areas other than axillary (1.5)

### DOSAGE AND ADMINISTRATION

- Follow indication-specific dosage and administration recommendations. In a 3 month interval, do not exceed a total dose of:
  - Adults: 400 Units
  - Pediatrics: the lesser of 10 Units/kg or 340 Units (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)
- Adult 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)
- Adult Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)

- Pediatric Upper Limb Spasticity: Recommended total dose 3 Units/kg to 6 Units/kg (maximum 200 Units) divided among affected muscles (2.6)
- Pediatric Lower Limb Spasticity: Recommended total dose 4 Units/kg to 8 Units/kg (maximum 300 Units) divided among affected muscles (2.6)
- 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 naïve patients (2.7)
- Axillary Hyperhidrosis: 50 Units per axilla (2.8)
- Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.9)
- Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX (2.10)

### DOSAGE FORMS AND STRENGTHS

For Injection: 100 Units or 200 Units vacuum-dried powder in a single-dose vial (3)

### CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4, 5.4, 6)
- Infection at the proposed injection site (4)
- Intradetrusor Injections: Urinary tract infection or urinary retention (4)

### WARNINGS AND PRECAUTIONS

- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.1, 5.6)
- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.2, 11)
- 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
- Adult Spasticity: pain in extremity
- Pediatric Spasticity: upper respiratory tract infection
- 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 1-800-678-1605 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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 (7.1, 7.4)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 09/2020**

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- 1.2 Chronic Migraine
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- 2.3 Bladder Dysfunction
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- 2.5 Adult Spasticity
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- 2.7 Cervical Dystonia
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- 2.9 Blepharospasm
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\* Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, 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 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* (5.1)].

## 1 INDICATIONS AND USAGE

### 1.1 Bladder Dysfunction

#### *Overactive Bladder*

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

#### *Detrusor Overactivity associated with a Neurologic Condition*

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults 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).

#### *Limitations of Use*

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

### 1.3 Spasticity

BOTOX is indicated for the treatment of spasticity in patients 2 years of age and older.

#### *Limitations of Use*

BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture.

### 1.4 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.

### 1.5 Primary Axillary Hyperhidrosis

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

#### *Limitations of Use*

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

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

### 1.6 Blepharospasm and Strabismus

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

## 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* (5.2) 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. In pediatric patients, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval [see *Dosage and Administration* (2.6)].

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.

Do not use BOTOX and contact Allergan (1-800-890-4345) if:

- the carton labeling does not contain an intact seal with a translucent silver Allergan logo (on both ends of the carton) or the seal has a black circle with a diagonal line through it (i.e., prohibition sign),
- the vial label does not contain a holographic film containing the name “Allergan” within rainbow colored horizontal lines, or
- the U.S. License number 1145 is not present on the vial label and carton labeling [see *How Supplied/Storage and Handling* (16)].

### 2.2 Preparation and Dilution Technique

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

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

| Diluent* Added to 100 Unit Vial | Resulting Dose Units per 0.1 mL | Diluent* Added to 200 Unit Vial | Resulting Dose Units per 0.1 mL |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 1 mL                            | 10 Units                        | 1 mL                            | 20 Units                        |
| 2 mL                            | 5 Units                         | 2 mL                            | 10 Units                        |
| 4 mL                            | 2.5 Units                       | 4 mL                            | 5 Units                         |
| 8 mL                            | 1.25 Units                      | 8 mL                            | 2.5 Units                       |
| 10 mL                           | 1 Unit                          | 10 mL                           | 2 Units                         |

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

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

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

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

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

## 2.3 Bladder Dysfunction

### General

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

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

Appropriate caution should be exercised when performing a cystoscopy.

### Overactive Bladder

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

The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Dispose of any unused saline.

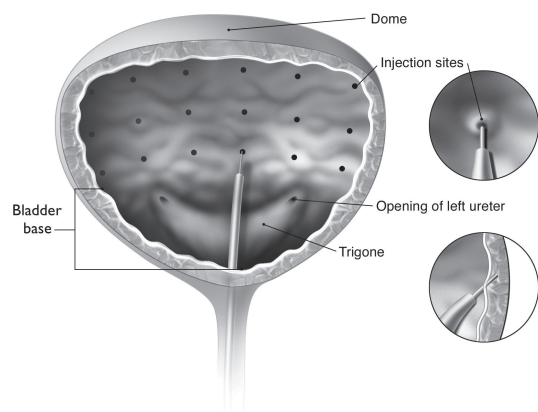
Reconstituted BOTOX (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

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

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

**Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity Associated with a Neurologic Condition**



## Detrusor Overactivity associated with a Neurologic Condition

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

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

### 200 Unit Vial of BOTOX

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

### 100 Unit Vial of BOTOX

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

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

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

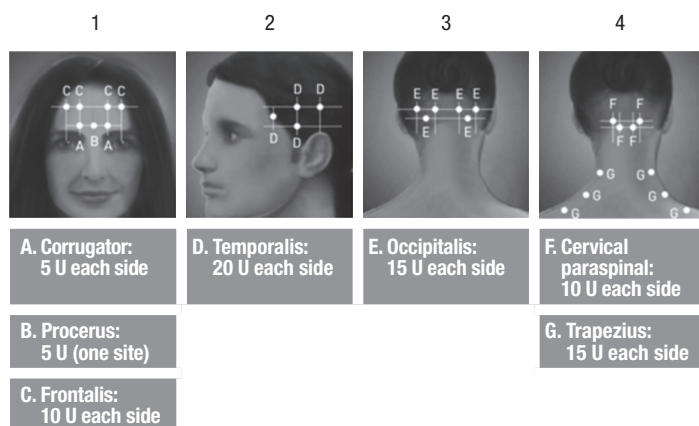
The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

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

## 2.4 Chronic Migraine

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

**Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine**



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

| Head/Neck Area                                | Recommended Dose (Number of Sites <sup>a</sup> ) |
|---|--|
| Frontalis <sup>b</sup>                        | 20 Units divided in 4 sites                      |
| Corrugator <sup>b</sup>                       | 10 Units divided in 2 sites                      |
| Procerus                                      | 5 Units in 1 site                                |
| Occipitalis <sup>b</sup>                      | 30 Units divided in 6 sites                      |
| Temporalis <sup>b</sup>                       | 40 Units divided in 8 sites                      |
| Trapezius <sup>b</sup>                        | 30 Units divided in 6 sites                      |
| Cervical Paraspinal Muscle Group <sup>b</sup> | 20 Units divided in 4 sites                      |
| <b>Total Dose:</b>                            | <b>155 Units divided in 31 sites</b>             |

<sup>a</sup> Each IM injection site = 0.1 mL = 5 Units BOTOX

<sup>b</sup> Dose distributed bilaterally

## 2.5 Adult Spasticity

### General

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

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

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

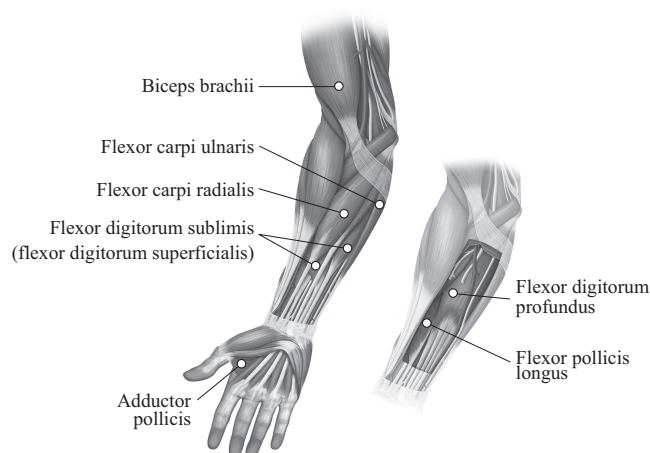
### Adult Upper Limb Spasticity

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 Adult Upper Limb Spasticity**

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

**Figure 2: Injection Sites for Adult Upper Limb Spasticity**



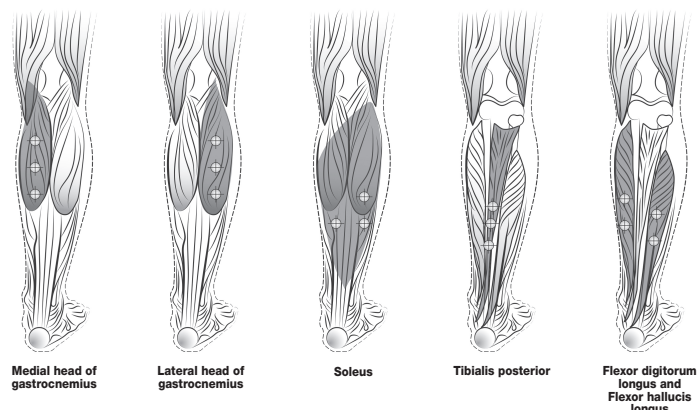
### Adult Lower Limb Spasticity

The recommended dose for treating adult 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 Adult Lower Limb Spasticity**

| Muscle                     | Recommended Dose Total Dosage (Number of Sites) |
|----------------------------|---|
| Gastrocnemius medial head  | 75 Units divided in 3 sites                     |
| Gastrocnemius lateral head | 75 Units divided in 3 sites                     |
| Soleus                     | 75 Units divided in 3 sites                     |
| Tibialis Posterior         | 75 Units divided in 3 sites                     |
| Flexor hallucis longus     | 50 Units divided in 2 sites                     |
| Flexor digitorum longus    | 50 Units divided in 2 sites                     |

**Figure 3: Injection Sites for Adult Lower Limb Spasticity**



## 2.6 Pediatric Spasticity

### General

Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended. When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval [see *Boxed Warning and Warnings and Precautions (5.1, 5.6)*]. Additional *general* adult spasticity dosing information is also applicable to pediatric spasticity patients [see *Dosage and Administration (2.5)*].

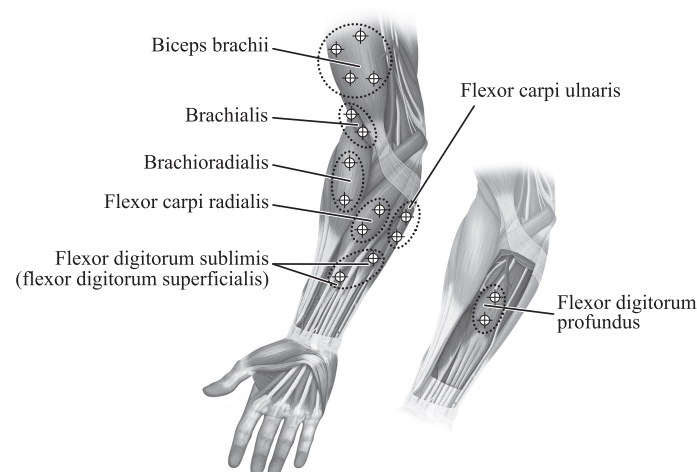
### Pediatric Upper Limb Spasticity

The recommended dose for treating pediatric upper limb spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles (see Table 5 and Figure 4). The total dose of BOTOX administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower.

**Table 5: BOTOX Dosing by Muscle for Pediatric Upper Limb Spasticity**

| Muscle                     | Recommended Dose and Number of Sites          |
|----------------------------|---|
| Biceps Brachii             | 1.5 Units/kg to 3 Units/kg divided in 4 sites |
| Brachialis                 | 1 Unit/kg to 2 Units/kg divided in 2 sites    |
| Brachioradialis            | 0.5 Units/kg to 1 Unit/kg divided in 2 sites  |
| Flexor Carpi Radialis      | 1 Unit/kg to 2 Units/kg divided in 2 sites    |
| Flexor Carpi Ulnaris       | 1 Unit/kg to 2 Units/kg divided in 2 sites    |
| Flexor Digitorum Profundus | 0.5 Units/kg to 1 Unit/kg divided in 2 sites  |
| Flexor Digitorum Sublimis  | 0.5 Units/kg to 1 Unit/kg divided in 2 sites  |

**Figure 4: Injection Sites for Pediatric Upper Limb Spasticity**





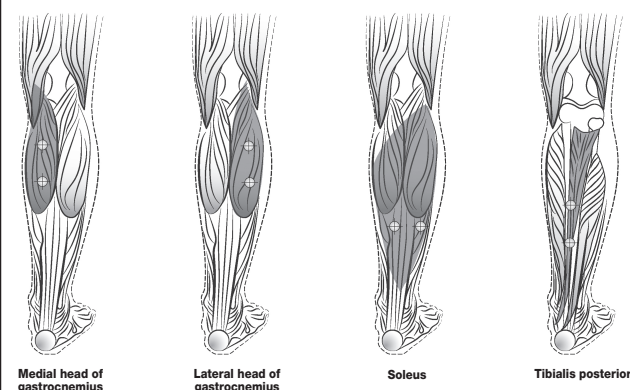
### Pediatric Lower Limb Spasticity

The recommended dose for treating pediatric lower limb spasticity is 4 Units/kg to 8 Units/kg divided among the affected muscles (see Table 6 and Figure 5). The total dose of BOTOX administered per treatment session in the lower limb should not exceed 8 Units/kg or 300 Units, whichever is lower.

**Table 6: BOTOX Dosing by Muscle for Pediatric Lower Limb Spasticity**

| Muscle                     | Recommended Dose Total Dosage (Number of Sites) |
|----------------------------|---|
| Gastrocnemius medial head  | 1 Unit/kg to 2 Units/kg divided in 2 sites      |
| Gastrocnemius lateral head | 1 Unit/kg to 2 Units/kg divided in 2 sites      |
| Soleus                     | 1 Unit/kg to 2 Units/kg divided in 2 sites      |
| Tibialis Posterior         | 1 Unit/kg to 2 Units/kg divided in 2 sites      |

**Figure 5: Injection Sites for Pediatric Lower Limb Spasticity**



### 2.7 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 (14.6)].

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 (5.1, 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.

### 2.8 Primary Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Using a sterile 30 gauge needle, 50 Units of BOTOX (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

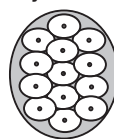
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

#### Instructions for the Minor's Iodine-Starch Test Procedure:

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

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 6.

**Figure 6: Injection Pattern for Primary Axillary Hyperhidrosis**



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

### 2.9 Blepharospasm

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

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

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

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

### 2.10 Strabismus

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

The volume of BOTOX injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX [see Dosage and Administration (2.2)] typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

#### Initial Doses in Units

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

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

#### Subsequent Doses for Residual or Recurrent Strabismus

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

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

### 3 DOSAGE FORMS AND STRENGTHS

For Injection: sterile 100 Units or 200 Units vacuum-dried powder in single-dose vials for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection, USP prior to injection.

4     **CONTRAINDICATIONS**

BOTOX is contraindicated:

- In patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation [see *Warnings and Precautions* (5.4)].
- In the presence of infection at the proposed injection site(s).
- For intradetrusor injection in patients with a urinary tract infection; or in patients with urinary retention or post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC) [see *Warnings and Precautions* (5.12, 5.13)].

5     **WARNINGS AND PRECAUTIONS**

5.1   **Spread of Toxin Effect**

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

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

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

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

5.3   **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* (5.1, 5.6)].

5.6   **Dysphagia and Breathing Difficulties**

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing [see *Warnings and Precautions* (5.1)].

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* (5.1)].

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 adult patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV<sub>1</sub> 40-80% of predicted value and FEV<sub>1</sub>/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 7).

**Table 7: Event Rate Per Patient Treatment Cycle Among Adult Upper Limb Spasticity 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**

|         | BOTOX<br>360 Units |      | BOTOX<br>240 Units |      | Placebo |      |
|---------|--------------------|------|--------------------|------|---------|------|
|         | ≥15%               | ≥20% | ≥15%               | ≥20% | ≥15%    | ≥20% |
| Week 1  | 4%                 | 0%   | 3%                 | 0%   | 7%      | 3%   |
| Week 6  | 7%                 | 4%   | 4%                 | 2%   | 2%      | 2%   |
| Week 12 | 10%                | 5%   | 2%                 | 1%   | 4%      | 1%   |

Differences from placebo were not statistically significant

In adult spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo [see *Warnings and Precautions* (5.10)].

In a double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 8).

**Table 8: 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**

|         | BOTOX<br>200 Units |           | Placebo   |           |
|---------|--------------------|-----------|-----------|-----------|
|         | ≥15%               | ≥20%      | ≥15%      | ≥20%      |
| Week 2  | 0/15 (0%)          | 0/15 (0%) | 1/11 (9%) | 0/11 (0%) |
| Week 6  | 2/13 (15%)         | 1/13 (8%) | 0/12 (0%) | 0/12 (0%) |
| Week 12 | 0/12 (0%)          | 0/12 (0%) | 0/7 (0%)  | 0/7 (0%)  |

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 adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In adult 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 reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

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

**Table 9: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB**

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

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 10.

**Table 10: Proportion of Patients Experiencing Urinary Retention Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus**

|                   | Patients with Diabetes |                | Patients without Diabetes |                 |
|-------------------|------------------------|----------------|---------------------------|-----------------|
|                   | BOTOX 100 Units (N=81) | Placebo (N=69) | BOTOX 100 Units (N=526)   | Placebo (N=516) |
| Urinary retention | 12.3% (n=10)           | 0              | 6.3% (n=33)               | 0.6% (n=3)      |

*Detrusor Overactivity associated with a Neurologic Condition*  
In two double-blind, placebo-controlled trials in patients with detrusor overactivity associated with a neurologic condition (NDO-1 and NDO-2), the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX 200 Units or placebo is shown in Table 11. The duration of post-injection catheterization for those who developed urinary retention is also shown.

**Table 11: Proportion of Patients Not Using CIC at Baseline and then Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials**

| Timepoint   | BOTOX 200 Units (N=108) | Placebo (N=104) |
|---|-------------------------|-----------------|
| <b>Proportion of Patients Catheterizing for Urinary Retention</b> |                         |                 |
| At any time during complete treatment cycle                       | 30.6% (n=33)            | 6.7% (n=7)      |
| <b>Duration of Catheterization for Urinary Retention (Days)</b>   |                         |                 |
| Median  | 289                     | 358             |
| Min, Max  | 1, 530                  | 2, 379          |

Among patients not using CIC at baseline, those with Multiple Sclerosis (MS) were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 12).

**Table 12: 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**

| Timepoint                                   | MS                     |                | SCI                    |                |
|---|------------------------|----------------|------------------------|----------------|
|   | BOTOX 200 Units (N=86) | Placebo (N=88) | BOTOX 200 Units (N=22) | Placebo (N=16) |
| At any time during complete treatment cycle | 31% (n=27)             | 5% (n=4)       | 27% (n=6)              | 19% (n=3)      |

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

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

- 6 ADVERSE REACTIONS**  
The following adverse reactions to BOTOX (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:
- Spread of Toxin Effects [see *Warnings and Precautions* (5.1)]
  - Serious Adverse Reactions with Unapproved Use [see *Warnings and Precautions* (5.3)]
  - Hypersensitivity Reactions [see *Contraindications* (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 Treated for Spasticity or for Detrusor Overactivity Associated with a Neurologic Condition [see *Warnings and Precautions* (5.7)]
  - Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm [see *Warnings and Precautions* (5.8)]
  - Retrobulbar 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* (5.1)].

*Overactive Bladder*  
Table 13 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 13: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Often than in Placebo-Treated Patients Within the First 12 Weeks after Intraderusor Injection, in Double-Blind, Placebo-Controlled Clinical Trials in Patients with OAB**

| Adverse Reactions       | BOTOX 100 Units (N=552) % | Placebo (N=542) % |
|-------------------------|---------------------------|-------------------|
| Urinary tract infection | 18                        | 6                 |
| Dysuria                 | 9                         | 7                 |
| Urinary retention       | 6                         | 0                 |
| Bacteriuria             | 4                         | 2                 |
| Residual urine volume*  | 3                         | 0                 |

\* 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 14.

**Table 14: Proportion of Patients Experiencing Urinary Tract Infection Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus**

|                               | Patients with Diabetes   |                  | Patients without Diabetes |                   |
|-------------------------------|--------------------------|------------------|---------------------------|-------------------|
|                               | BOTOX 100 Units (N=81) % | Placebo (N=69) % | BOTOX 100 Units (N=526) % | Placebo (N=516) % |
| Urinary tract infection (UTI) | 31                       | 12               | 26                        | 10                |

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

#### *Detrusor Overactivity associated with a Neurologic Condition*

Table 15 presents the most frequently reported adverse reactions in the double-blind, placebo-controlled studies within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX 200 Units.

**Table 15: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients Within the First 12 Weeks after Intraderusor Injection in Double-Blind, Placebo-Controlled Clinical Trials**

| Adverse Reactions       | BOTOX 200 Units (N=262) % | Placebo (N=272) % |
|-------------------------|---------------------------|-------------------|
| Urinary tract infection | 24                        | 17                |
| Urinary retention       | 17                        | 3                 |
| Hematuria               | 4                         | 3                 |

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 16 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 16: Adverse Reactions Reported in a Post Approval Study (NDO-3) by >2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients Within the First 12 Weeks after Intraderusor Injection**

| Adverse Reactions       | BOTOX 100 Units (N=66) % | Placebo (N=78) % |
|-------------------------|--------------------------|------------------|
| Urinary tract infection | 26                       | 6                |
| Bacteriuria             | 9                        | 5                |
| Urinary retention       | 15                       | 1                |
| Dysuria                 | 5                        | 1                |
| Residual urine volume*  | 17                       | 1                |

\* 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%), residual urine volume\* (17%), dysuria (9%), and hematuria (5%).

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

#### *Chronic Migraine*

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

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 17.

**Table 17: 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**

| Adverse Reactions                                    | BOTOX 155 Units-195 Units (N=687) % | Placebo (N=692) % |
|--|-------------------------------------|-------------------|
| Nervous system disorders                             |                                     |                   |
| Headache   | 5                                   | 3                 |
| Migraine   | 4                                   | 3                 |
| Facial paresis                                       | 2                                   | 0                 |
| Eye disorders  |                                     |                   |
| Eyelid ptosis  | 4                                   | <1                |
| Infections and Infestations                          |                                     |                   |
| Bronchitis   | 3                                   | 2                 |
| Musculoskeletal and connective tissue disorders      |                                     |                   |
| Neck pain  | 9                                   | 3                 |
| Musculoskeletal stiffness                            | 4                                   | 1                 |
| Muscular weakness                                    | 4                                   | <1                |
| Myalgia  | 3                                   | 1                 |
| Musculoskeletal pain                                 | 3                                   | 1                 |
| Muscle spasms  | 2                                   | 1                 |
| General disorders and administration site conditions |                                     |                   |
| Injection site pain                                  | 3                                   | 2                 |
| Vascular Disorders                                   |                                     |                   |
| Hypertension   | 2                                   | 1                 |

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.

#### *Adult Upper Limb Spasticity*

The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 18.

**Table 18: 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**

| Adverse Reactions                                    | BOTOX 251 Units-360 Units (N=115) % | BOTOX 150 Units-250 Units (N=188) % | BOTOX <150 Units (N=54) % | Placebo (N=182) % |
|--|-------------------------------------|-------------------------------------|---------------------------|-------------------|
| Gastrointestinal disorder                            |                                     |                                     |                           |                   |
| Nausea   | 3                                   | 2                                   | 2                         | 1                 |
| General disorders and administration site conditions |                                     |                                     |                           |                   |
| Fatigue  | 3                                   | 2                                   | 2                         | 0                 |
| Infections and infestations                          |                                     |                                     |                           |                   |
| Bronchitis   | 3                                   | 2                                   | 0                         | 1                 |
| Musculoskeletal and connective tissue disorders      |                                     |                                     |                           |                   |
| Pain in extremity                                    | 6                                   | 5                                   | 9                         | 4                 |
| Muscular weakness                                    | 0                                   | 4                                   | 2                         | 1                 |

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.

### Adult Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 19. 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 19: 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)**

| Adverse Reactions                                    | BOTOX<br>(N=231) % | Placebo<br>(N=233) % |
|--|--------------------|----------------------|
| Musculoskeletal and connective tissue disorders      |                    |                      |
| Arthralgia   | 3                  | 1                    |
| Back pain  | 3                  | 2                    |
| Myalgia  | 2                  | 1                    |
| Infections and infestations                          |                    |                      |
| Upper respiratory tract infection                    | 2                  | 1                    |
| General disorders and administration site conditions |                    |                      |
| Injection site pain                                  | 2                  | 1                    |

### Pediatric Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric patients 2 to 17 years of age with upper limb spasticity appear in Table 20. In a double-blind, placebo-controlled trial (Study 1), 78 patients were treated with 3 Units/kg of BOTOX, and 77 patients received 6 Units/kg to a maximum dose of 200 Units of BOTOX, and were compared to 79 patients who received placebo [see *Clinical Studies* (14.5)]. Patients were followed for an average of 91 days after injection.

**Table 20: Adverse Reactions Reported by ≥2% of BOTOX 6 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 1)**

| Adverse Reactions                                    | BOTOX<br>6 Units/kg<br>(N=77) % | BOTOX<br>3 Units/kg<br>(N=78) % | Placebo<br>(N=79) % |
|--|---------------------------------|---------------------------------|---------------------|
| Infections and infestations                          |                                 |                                 |                     |
| Upper respiratory tract infection*                   | 17                              | 10                              | 9                   |
| General disorders and administration site conditions |                                 |                                 |                     |
| Injection site pain                                  | 4                               | 3                               | 1                   |
| Gastrointestinal disorders                           |                                 |                                 |                     |
| Nausea   | 4                               | 0                               | 0                   |
| Constipation   | 3                               | 0                               | 1                   |
| Respiratory, thoracic and mediastinal disorders      |                                 |                                 |                     |
| Rhinitis   | 4                               | 0                               | 1                   |
| Nasal congestion                                     | 3                               | 0                               | 1                   |
| Nervous system disorders                             |                                 |                                 |                     |
| Seizure**  | 5                               | 1                               | 0                   |

\* Includes upper respiratory tract infection and viral upper respiratory tract infection

\*\* Includes seizure and partial seizure

### Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric patients 2 to 17 years of age with lower limb spasticity appear in Table 21. In a double-blind, placebo-controlled trial (Study 2), 126 patients were treated with 4 Units/kg of BOTOX, and 128 patients received 8 Units/kg to a maximum dose of 300 Units of BOTOX, and were compared to 128 patients who received placebo [see *Clinical Studies* (14.5)]. Patients were followed for an average of 89 days after injection.

**Table 21: Adverse Reactions Reported by ≥2% of BOTOX 8 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 2)**

| Adverse Reactions                                    | BOTOX<br>8 Units/kg<br>(N=128) % | BOTOX<br>4 Units/kg<br>(N=126) % | Placebo<br>(N=128) % |
|--|----------------------------------|----------------------------------|----------------------|
| General disorders and administration site conditions |                                  |                                  |                      |
| Injection site erythema                              | 2                                | 0                                | 0                    |
| Injection site pain                                  | 2                                | 2                                | 0                    |
| Respiratory, thoracic and mediastinal disorders      |                                  |                                  |                      |
| Oropharyngeal pain                                   | 2                                | 0                                | 1                    |
| Injury, poisoning and procedural complications       |                                  |                                  |                      |
| Ligament sprain                                      | 2                                | 1                                | 0                    |
| Skin abrasion  | 2                                | 0                                | 0                    |
| Metabolism and nutrition disorders                   |                                  |                                  |                      |
| Decreased appetite                                   | 2                                | 0                                | 0                    |

### Cervical Dystonia

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles [see *Warnings and Precautions* (5.1, 5.6)].

The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea [see *Warnings and Precautions* (5.1, 5.6)]. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms [see *Warnings and Precautions* (5.6)].

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of BOTOX for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

### Primary Axillary Hyperhidrosis

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

Extraocular 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 one Phase 3 study and the open-label extension study in patients with pediatric lower limb spasticity, neutralizing antibodies developed in 2 of 264 patients (0.8%) treated with BOTOX for up to 5 treatment cycles. Both patients continued to experience clinical benefit following subsequent BOTOX treatments.

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 detrusor overactivity associated with neurologic condition patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX



200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to BOTOX in the remaining 2 patients is not known.

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

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

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; dry eye; eyelid edema (following periorcular injection); hyperhidrosis; hypoaesthesia; localized muscle twitching; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

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

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

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

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

7.2 Anticholinergic Drugs

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

7.3 Other Botulinum Neurotoxin Products

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

7.4 Muscle Relaxants

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX in pregnant women. In animal studies, administration of BOTOX during pregnancy resulted in adverse effects on fetal growth (decreased fetal weight and 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.

In a 12-week, multicenter, double-blind, placebo-controlled clinical trial, 123 adolescent patients (ages 12 to below 18 years) with chronic migraine were randomized to receive BOTOX 74 Units, BOTOX 155 Units, or placebo, for one injection cycle. This trial did not establish the efficacy of BOTOX, compared with placebo, for the prophylaxis of headaches in adolescents with chronic migraine.

Spasticity

Safety and effectiveness have been established in pediatric patients 2 to 17 years of age [see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Studies (14.5)]. The safety and effectiveness of BOTOX have been established by evidence from adequate and well-controlled studies of BOTOX in patients 2 to 17 years of age with upper and lower limb spasticity.

Safety and effectiveness in pediatric patients below the age of 2 years have not been established [see Boxed Warning and Warnings and Precautions (5.1)].

Juvenile Animal Data

In a study in which juvenile rats received intramuscular injection of BOTOX (0, 8, 16, or 24 Units/kg) every other week from postnatal day 21 for 12 weeks, changes in bone size/geometry associated with decreased bone density and bone mass were observed at all doses, in association with limb disuse, decreased muscle contraction, and decreased body weight gain. Impairment of fertility and male reproductive organ histopathology (degeneration of seminiferous tubules of the testis) were observed at the mid and high doses. Bone and male reproductive organ effects showed evidence of reversibility after dosing cessation. The no-effect dose for adverse developmental effects in juvenile animals (8 Units/kg) is similar to the human dose (400 Units) on a body weight (kg) basis.

Axillary Hyperhidrosis

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

Cervical Dystonia

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

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 adult 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 adult patients younger than 65 years of age.

In clinical studies of BOTOX across other indications, no overall differences in safety were observed between elderly patients and younger adult patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified differences in responses between the elderly and younger adult 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 UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 22). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to adult patients younger than 65 years of age in these studies.

Table 22: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-Controlled Treatment, Placebo-Controlled Clinical Trials in Patients with OAB

|                         | <65 Years                 |                   | 65 to 74 Years            |                   | ≥75 Years                |                  |
|-------------------------|---------------------------|-------------------|---------------------------|-------------------|--------------------------|------------------|
| Adverse Reactions       | BOTOX 100 Units (N=344) % | Placebo (N=348) % | BOTOX 100 Units (N=169) % | Placebo (N=151) % | BOTOX 100 Units (N=94) % | Placebo (N=86) % |
| Urinary tract infection | 21                        | 7                 | 30                        | 13                | 38                       | 19               |
| Urinary retention       | 6                         | 0.6               | 8                         | 0                 | 9                        | 1                |

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



## 10 OVERDOSAGE

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

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see **Boxed Warning and Warnings and Precautions** (5.1, 5.6)]. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

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

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

## 11 DESCRIPTION

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

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD<sub>50</sub>) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

When injected intradermally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

### 12.3 Pharmacokinetics

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

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

#### Mutagenesis

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

### Impairment of Fertility

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

### 13.2 Animal Toxicology and/or Pharmacology

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

## 14 CLINICAL STUDIES

### 14.1 Overactive Bladder (OAB)

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Table 23 and Table 24, and Figure 7 and Figure 8.

**Table 23: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1**

|   | BOTOX<br>100 Units<br>(N=278) | Placebo<br>(N=272) | Treatment<br>Difference | p-value |
|---|-------------------------------|--------------------|-------------------------|---------|
| <b>Daily Frequency of Urinary Incontinence Episodes<sup>a</sup></b> |                               |                    |                         |         |
| Mean Baseline   | 5.5                           | 5.1                |                         |         |
| Mean Change* at Week 2  | -2.6                          | -1.0               | -1.6                    |         |
| Mean Change* at Week 6  | -2.8                          | -1.0               | -1.8                    |         |
| Mean Change* at Week 12**   | -2.5                          | -0.9               | -1.6<br>(-2.1, -1.2)    | <0.001  |
| <b>Daily Frequency of Micturition Episodes<sup>a</sup></b>          |                               |                    |                         |         |
| Mean Baseline   | 12.0                          | 11.2               |                         |         |
| Mean Change <sup>†</sup> at Week 12**                               | -1.9                          | -0.9               | -1.0<br>(-1.5, -0.6)    | <0.001  |
| <b>Volume Voided per Micturition<sup>a</sup> (mL)</b>               |                               |                    |                         |         |
| Mean Baseline   | 156                           | 161                |                         |         |
| Mean Change <sup>†</sup> at Week 12**                               | 38                            | 8                  | 30<br>(17, 43)          | <0.001  |

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

<sup>†</sup> 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

<sup>a</sup> Primary variable

<sup>b</sup> Secondary variable

**Table 24: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2**

|   | BOTOX<br>100 Units<br>(N=275) | Placebo<br>(N=269) | Treatment<br>Difference | p-value |
|---|-------------------------------|--------------------|-------------------------|---------|
| <b>Daily Frequency of Urinary Incontinence Episodes<sup>a</sup></b> |                               |                    |                         |         |
| Mean Baseline   | 5.5                           | 5.7                |                         |         |
| Mean Change* at Week 2  | -2.7                          | -1.1               | -1.6                    |         |
| Mean Change* at Week 6  | -3.1                          | -1.3               | -1.8                    |         |
| Mean Change* at Week 12**   | -3.0                          | -1.1               | -1.9<br>(-2.5, -1.4)    | <0.001  |
| <b>Daily Frequency of Micturition Episodes<sup>b</sup></b>          |                               |                    |                         |         |
| Mean Baseline   | 12.0                          | 11.8               |                         |         |
| Mean Change <sup>a</sup> at Week 12**                               | -2.3                          | -0.6               | -1.7<br>(-2.2, -1.3)    | <0.001  |
| <b>Volume Voided per Micturition<sup>b</sup> (mL)</b>               |                               |                    |                         |         |
| Mean Baseline   | 144                           | 153                |                         |         |
| Mean Change <sup>a</sup> at Week 12**                               | 40                            | 10                 | 31<br>(20, 41)          | <0.001  |

\* 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.

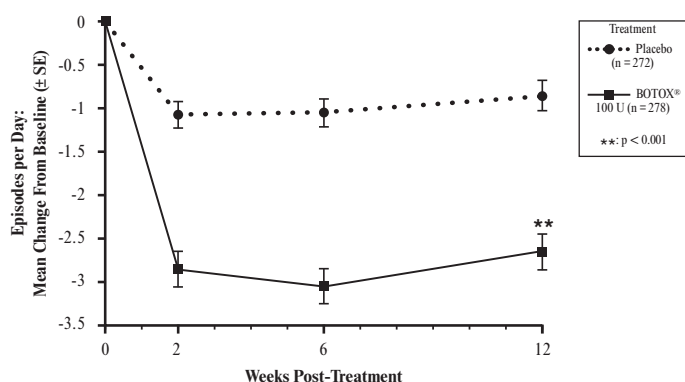
† LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

\*\* Primary timepoint

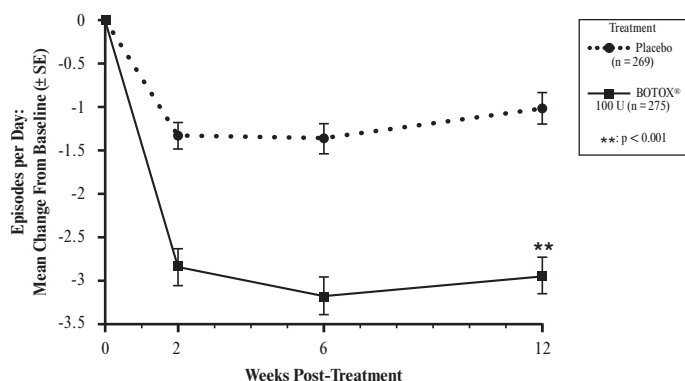
<sup>a</sup> Primary variable

<sup>b</sup> Secondary variable

**Figure 7: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes Following Intradetrusor Injection in Study OAB-1**



**Figure 8: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes Following Intradetrusor Injection in Study OAB-2**



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 Table 25 and Table 26, and Figure 9 and Figure 10.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

**Table 25: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH<sub>2</sub>O) Study NDO-1**

|   | BOTOX<br>200 Units | Placebo | Treatment<br>Difference* | p-value* |
|---|--------------------|---------|--------------------------|----------|
| <b>Weekly Frequency of Urinary Incontinence Episodes<sup>a</sup></b>  |                    |         |                          |          |
| N   | 134                | 146     |                          |          |
| Mean Baseline   | 32.3               | 28.3    |                          |          |
| Mean Change* at Week 2  | -15.3              | -10.0   | -5.3                     | —        |
| Mean Change* at Week 6**  | -19.9              | -10.6   | -9.2<br>(-13.1, -5.3)    | p<0.001  |
| Mean Change* at Week 12   | -19.8              | -8.8    | -11.0                    | —        |
| <b>Maximum Cystometric Capacity<sup>b</sup> (mL)</b>  |                    |         |                          |          |
| N   | 123                | 129     |                          |          |
| Mean Baseline   | 253.8              | 259.1   |                          |          |
| Mean Change* at Week 6**  | 135.9              | 12.1    | 123.9<br>(89.1, 158.7)   | p<0.001  |
| <b>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction<sup>b</sup> (cmH<sub>2</sub>O)</b> |                    |         |                          |          |
| N   | 41                 | 103     |                          |          |
| Mean Baseline   | 63.1               | 57.4    |                          |          |
| Mean Change* at Week 6**  | -28.1              | -3.7    | -24.4                    | —        |

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

\*\* Primary timepoint

<sup>a</sup> Primary endpoint

<sup>b</sup> Secondary endpoint

**Table 26: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH<sub>2</sub>O) in Study NDO-2**

|   | BOTOX 200 Units | Placebo | Treatment Difference* | p-value* |
|---|-----------------|---------|-----------------------|----------|
| <b>Weekly Frequency of Urinary Incontinence Episodes<sup>a</sup></b>  |                 |         |                       |          |
| N   | 91              | 91      |                       |          |
| Mean Baseline   | 32.7            | 36.8    |                       |          |
| Mean Change* at Week 2  | -18.0           | -7.9    | -10.1                 | —        |
| Mean Change* at Week 6**  | -19.6           | -10.8   | -8.8 (-14.5, -3.0)    | p=0.003  |
| Mean Change* at Week 12   | -19.6           | -10.7   | -8.9                  | —        |
| <b>Maximum Cystometric Capacity<sup>b</sup> (mL)</b>  |                 |         |                       |          |
| N   | 88              | 85      |                       |          |
| Mean Baseline   | 239.6           | 253.8   |                       |          |
| Mean Change* at Week 6**  | 150.8           | 2.8     | 148.0 (101.8, 194.2)  | p<0.001  |
| <b>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction<sup>b</sup> (cmH<sub>2</sub>O)</b> |                 |         |                       |          |
| N   | 29              | 68      |                       |          |
| Mean Baseline   | 65.6            | 43.7    |                       |          |
| Mean Change* at Week 6**  | -28.7           | 2.1     | -30.7                 | —        |

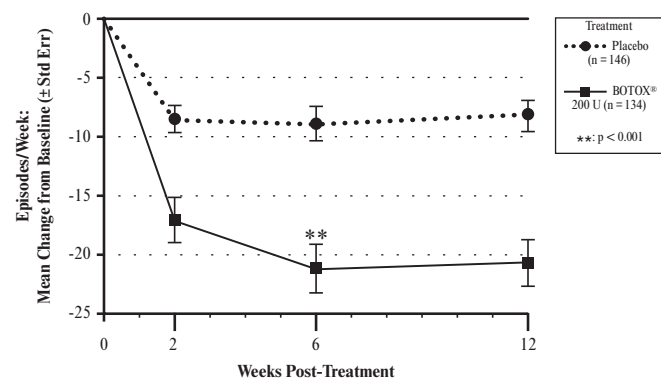
\* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.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

\*\* Primary timepoint

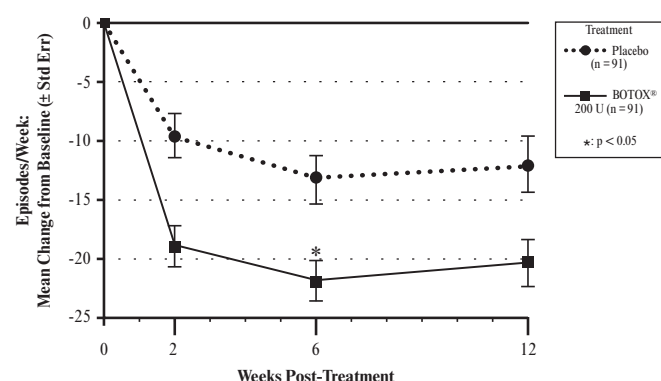
<sup>a</sup> Primary endpoint

<sup>b</sup> Secondary endpoint

**Figure 9: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-1**



**Figure 10: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2**



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 27.

**Table 27: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH<sub>2</sub>O) in Study NDO-3**

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

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

\*\* Primary timepoint

<sup>a</sup> Primary endpoint

<sup>b</sup> 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 28).

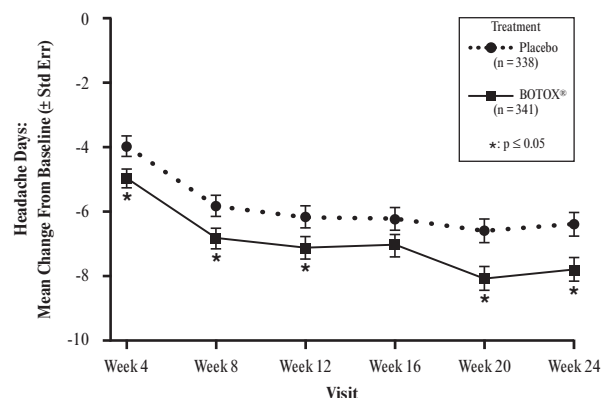
**Table 28: Week 24 Key Efficacy Variables for Study 1 and Study 2**

| Efficacy per 28 days  | Study 1       |                 | Study 2       |                 |
|---|---------------|-----------------|---------------|-----------------|
|   | BOTOX (N=341) | Placebo (N=338) | BOTOX (N=347) | Placebo (N=358) |
| Change from baseline in frequency of headache days                          | -7.8*         | -6.4            | -9.2*         | -6.9            |
| Change from baseline in total cumulative hours of headache on headache days | -107*         | -70             | -134*         | -95             |

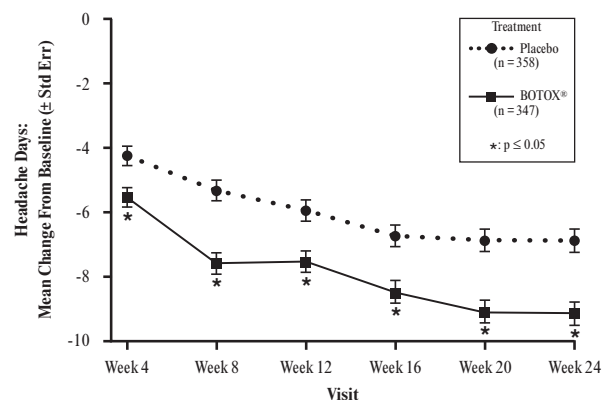
\* Significantly different from placebo (p<0.05)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 11), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 12), compared to placebo-treated patients.

**Figure 11: Mean Change from Baseline in Number of Headache Days for Study 1**



**Figure 12: Mean Change from Baseline in Number of Headache Days for Study 2**



#### 14.4 Adult Spasticity

##### Adult Upper Limb Spasticity

The efficacy of BOTOX for the treatment of adult 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 adult patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 29). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

**Table 29: BOTOX Dose and Injection Sites in Study 1**

| Muscles Injected                    | Volume (mL) | BOTOX (Units) | Number of Injection Sites |
|-------------------------------------|-------------|---------------|---------------------------|
| <b>Wrist</b>                        |             |               |                           |
| Flexor Carpi Radialis               | 1           | 50            | 1                         |
| Flexor Carpi Ulnaris                | 1           | 50            | 1                         |
| <b>Finger</b>                       |             |               |                           |
| Flexor Digitorum Profundus          | 1           | 50            | 1                         |
| Flexor Digitorum Sublimis           | 1           | 50            | 1                         |
| <b>Thumb</b>                        |             |               |                           |
| Adductor Pollicis <sup>a</sup>      | 0.4         | 20            | 1                         |
| Flexor Pollicis Longus <sup>a</sup> | 0.4         | 20            | 1                         |

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

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

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 30.

**Table 30: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1**

|   | BOTOX (N=64) | Placebo (N=62) |
|---|--------------|----------------|
| <b>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale<sup>†a</sup></b>   | -2.0*        | 0.0            |
| <b>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale<sup>††b</sup></b> | -1.0*        | 0.0            |
| <b>Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale<sup>††c</sup></b>  | -1.0         | -1.0           |
| <b>Median Physician Global Assessment of Response to Treatment<sup>††</sup></b>                     | 2.0*         | 0.0            |

<sup>†</sup> Primary endpoint at Week 6

<sup>††</sup> Secondary endpoints at Week 6

\* Significantly different from placebo (p≤0.05)

<sup>a</sup> BOTOX injected into both the flexor carpi radialis and ulnaris muscles

<sup>b</sup> BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

<sup>c</sup> BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 adult 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 31).

**Table 31: BOTOX Dose and Injection Sites in Study 2 and Study 3**

| Muscles Injected           | Total Dose                |                            |                             | Volume (mL) per site | Injection Sites (n) |
|----------------------------|---------------------------|----------------------------|-----------------------------|----------------------|---------------------|
|                            | BOTOX low dose (90 Units) | BOTOX mid dose (180 Units) | BOTOX high dose (360 Units) |                      |                     |
| <b>Wrist</b>               |                           |                            |                             |                      |                     |
| Flexor Carpi Ulnaris       | 10 Units                  | 20 Units                   | 40 Units                    | 0.4                  | 1                   |
| Flexor Carpi Radialis      | 15 Units                  | 30 Units                   | 60 Units                    | 0.6                  | 1                   |
| <b>Finger</b>              |                           |                            |                             |                      |                     |
| Flexor Digitorum Profundus | 7.5 Units                 | 15 Units                   | 30 Units                    | 0.3                  | 1                   |
| Flexor Digitorum Sublimis  | 7.5 Units                 | 15 Units                   | 30 Units                    | 0.3                  | 1                   |
| <b>Elbow</b>               |                           |                            |                             |                      |                     |
| Biceps Brachii             | 50 Units                  | 100 Units                  | 200 Units                   | 0.5                  | 4                   |

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 32.

**Table 32: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2**

|   | BOTOX low dose (90 Units) (N=21) | BOTOX mid dose (180 Units) (N=23) | BOTOX high dose (360 Units) (N=21) | Placebo (N=26) |
|---|----------------------------------|-----------------------------------|------------------------------------|----------------|
| <b>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale<sup>†b</sup></b>   | -1.5*                            | -1.0*                             | -1.5*                              | -1.0           |
| <b>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale<sup>††c</sup></b> | -0.5                             | -0.5                              | -1.0                               | -0.5           |
| <b>Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale<sup>††d</sup></b>  | -0.5                             | -1.0*                             | -0.5 <sup>a</sup>                  | -0.5           |
| <b>Median Physician Global Assessment of Response to Treatment</b>                                  | 1.0*                             | 1.0*                              | 1.0*                               | 0.0            |

<sup>†</sup> Primary endpoint at Week 6

<sup>††</sup> Secondary endpoints at Week 6

\* Significantly different from placebo (p≤0.05)

<sup>a</sup> p=0.053

<sup>b</sup> Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles

<sup>c</sup> Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

<sup>d</sup> Dose of BOTOX injected into biceps brachii muscle



Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 adult patients [BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger 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 31).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 33.

Table 33: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

|   | BOTOX<br>low dose<br>(90 Units)<br>(N=23) | BOTOX<br>mid dose<br>(180 Units)<br>(N=21) | BOTOX<br>high dose<br>(360 Units)<br>(N=22) | Placebo<br>(N=19) |
|---|---|--|---|-------------------|
| Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale <sup>b</sup>    | -1.0                                      | -1.0                                       | -1.5*                                       | -0.5              |
| Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale <sup>b,c</sup> | -1.0                                      | -1.0                                       | -1.0*                                       | -0.5              |
| Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale <sup>b</sup>    | -0.5                                      | -0.5                                       | -1.0*                                       | -0.5              |

† Primary endpoint at Week 4  
†† Secondary endpoints at Week 4  
\* Significantly different from placebo (p≤0.05)  
b Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles  
c Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles  
d Dose of BOTOX injected into biceps brachii muscle

Study 4 included 170 adult patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units in thumb muscles) or placebo (see Table 34). Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, adult 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 34). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

Table 34: BOTOX Dose and Injection Sites in Studies 4 and 5

| Muscles Injected        | Study 4       |             | Study 5                |                         |                      |                       | Number of Injection Sites for Studies 4 and 5 |
|-------------------------|---------------|-------------|------------------------|-------------------------|----------------------|-----------------------|---|
|                         | BOTOX (Units) | Volume (mL) | BOTOX low dose (Units) | BOTOX high dose (Units) | Volume low dose (mL) | Volume high dose (mL) |   |
| Thumb Adductor Pollicis | 20            | 0.4         | 15                     | 20                      | 0.3                  | 0.4                   | 1   |
| Flexor Pollicis Longus  | 20            | 0.4         | 15                     | 20                      | 0.3                  | 0.4                   | 1   |

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

Table 35: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

|  | BOTOX<br>(N=66) | Placebo<br>(N=57) |
|--|-----------------|-------------------|
| Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale <sup>††</sup> | -1.0*           | 0.0               |
| Median Physician Global Assessment of Response to Treatment <sup>††</sup>                            | 2.0*            | 0.0               |

†† Secondary endpoints at Week 6  
\* Significantly different from placebo (p≤0.001)  
a 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 36.

Table 36: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

|   | BOTOX<br>low dose<br>(30 Units)<br>(N=14) | Placebo<br>low dose<br>(N=9) | BOTOX<br>high dose<br>(40 Units)<br>(N=43) | Placebo<br>high dose<br>(N=23) |
|---|---|------------------------------|--|--------------------------------|
| Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale <sup>†††</sup> | -1.0                                      | -1.0                         | -0.5*                                      | 0.0                            |
| Median Change from Baseline in Clinical Global Impression Score by Physician <sup>††</sup>            | 1.0                                       | 0.0                          | 2.0*                                       | 0.0                            |

†† Secondary endpoint at Week 6  
††† Other endpoint at Week 6  
\* Significantly different from placebo (p≤0.010)  
a BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

**Adult Lower Limb Spasticity**  
The efficacy and safety of BOTOX for the treatment of adult lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke adult 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 37) 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 37: BOTOX Dose and Injection Sites in Study 6

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

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.

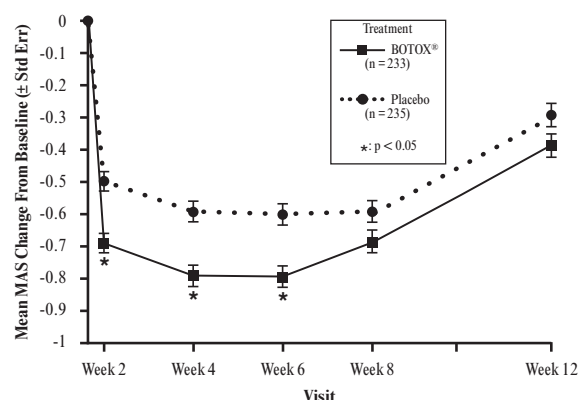
Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 38).

Table 38: Co-Primary Efficacy Endpoints Results in Study 6 (Intent-To-Treat Population)

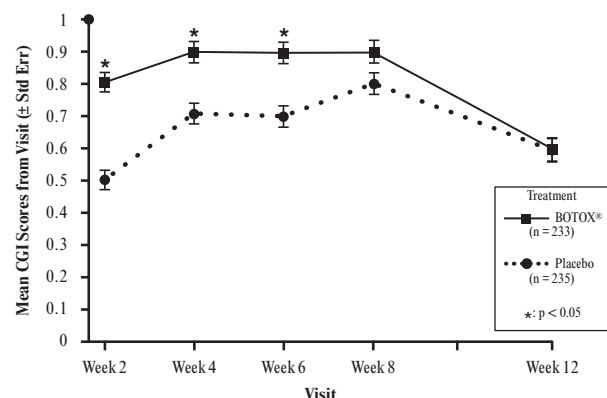
|  | BOTOX<br>300 to 400 Units<br>(N=233) | Placebo<br>(N=235) |
|--|--------------------------------------|--------------------|
| <b>Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale</b> |                                      |                    |
| Week 4 and 6 Average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

\* Significantly different from placebo (p<0.05)  
Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 13) and CGI (see Figure 14) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

**Figure 13: Modified Ashworth Scale Ankle Score for Study 6 – Mean Change from Baseline by Visit**



**Figure 14: Clinical Global Impression by Physician for Study 6 – Mean Scores by Visit**



## 14.5 Pediatric Spasticity

### Pediatric Upper Limb Spasticity

The efficacy and safety of BOTOX for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 1 (NCT01603602), a randomized, multi-center, double-blind, placebo-controlled study. Study 1 included 234 pediatric patients (78 BOTOX 3 Units/kg, 77 BOTOX 6 Units/kg, and 79 placebo) with upper limb spasticity (modified Ashworth Scale elbow or wrist score of at least 2) because of cerebral palsy or stroke. A total dose of 3 Units/kg BOTOX (maximum 100 Units), 6 Units/kg BOTOX (maximum 200 Units), or placebo was injected intramuscularly and divided between the elbow or wrist and finger muscles (see Table 39). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

**Table 39: BOTOX Dose and Injection Sites in Study 1**

| Muscles Injected                | BOTOX 3 Units/kg* (maximum Units per muscle) | BOTOX 6 Units/kg** (maximum Units per muscle) | Number of Injection Sites |
|---------------------------------|--|---|---------------------------|
| <b>Elbow Flexor Muscles</b>     |  |   |                           |
| Biceps                          | 1.5 Units/kg (50 Units)                      | 3 Units/kg (100 Units)                        | 4                         |
| Brachialis                      | 1 Unit/kg (30 Units)                         | 2 Units/kg (60 Units)                         | 2                         |
| Brachioradialis                 | 0.5 Units/kg (20 Units)                      | 1 Unit/kg (40 Units)                          | 2                         |
| <b>Wrist and Finger Muscles</b> |  |   |                           |
| Flexor carpi radialis           | 1 Unit/kg (25 Units)                         | 2 Units/kg (50 Units)                         | 2                         |
| Flexor carpi ulnaris            | 1 Unit/kg (25 Units)                         | 2 Units/kg (50 Units)                         | 2                         |
| Flexor digitorum profundus      | 0.5 Units/kg (25 Units)                      | 1 Unit/kg (50 Units)                          | 2                         |
| Flexor digitorum sublimis       | 0.5 Units/kg (25 Units)                      | 1 Unit/kg (50 Units)                          | 2                         |

\* Did not exceed a total dose of 100 Units

\*\* Did not exceed a total dose of 200 Units

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) principal muscle group score (elbow or wrist) at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (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 (-4=very marked worsening to +4=very marked improvement).

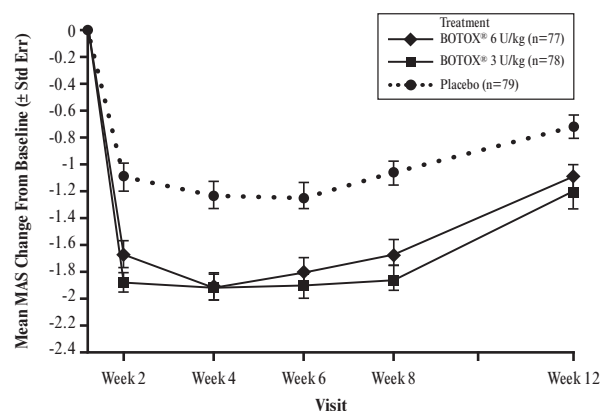
Compared to placebo, significant improvements in MAS change from baseline were observed at all timepoints for BOTOX-treated patients (see Table 40, Figure 15 and Figure 16). Although CGI scores numerically favored BOTOX over placebo, the difference was not statistically significant.

**Table 40: Co-Primary Efficacy Endpoints Results in Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population)**

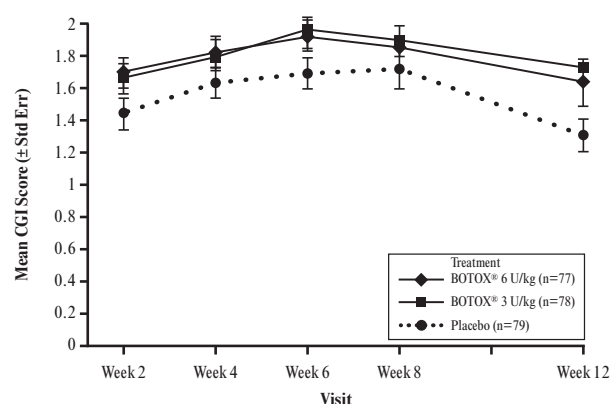
|  | BOTOX 3 Units/kg (N=78) | BOTOX 6 Units/kg (N=77) | Placebo (N=79) |
|--|-------------------------|-------------------------|----------------|
| <b>Mean Change from Baseline in Principal Muscle Group (Elbow or Wrist) on the modified Ashworth Scale</b> |                         |                         |                |
| Week 4 and 6 Average   | -1.92*                  | -1.87*                  | -1.21          |
| <b>Mean Clinical Global Impression Score</b>   |                         |                         |                |
| Week 4 and 6 Average   | 1.88                    | 1.87                    | 1.66           |

\* Nominal p value <0.05

**Figure 15: Modified Ashworth Scale Score for Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) – Mean Change from Baseline by Visit**



**Figure 16: Clinical Global Impression of Overall Change for Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) – Mean Scores by Visit**



### Pediatric Lower Limb Spasticity

The efficacy and safety of BOTOX for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 2 (NCT01603628), a randomized, multi-center, double-blind, placebo-controlled study. Study 2 included 381 pediatric patients (125 BOTOX 4 Units/kg, 127 BOTOX 8 Units/kg, and 129 placebo) with lower limb spasticity (modified Ashworth Scale ankle score of at least 2) because of cerebral palsy. A total dose of 4 Units/kg BOTOX (maximum 150 Units), 8 Units/kg BOTOX (maximum 300 Units), or placebo was injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior (see Table 41). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

Table 41: BOTOX Dose and Injection Sites in Study 2

| Muscles Injected               | BOTOX<br>4 Units/kg*<br>(maximum<br>Units<br>per muscle) | BOTOX<br>8 Units/kg**<br>(maximum<br>Units<br>per muscle) | Number of<br>Injection Sites |
|--------------------------------|--|---|------------------------------|
| <b>Mandatory Ankle Muscles</b> |  |   |                              |
| Gastrocnemius medial head      | 1 Unit/kg<br>(37.5 Units)                                | 2 Units/kg<br>(75 Units)                                  | 2                            |
| Gastrocnemius lateral head     | 1 Unit/kg<br>(37.5 Units)                                | 2 Units/kg<br>(75 Units)                                  | 2                            |
| Soleus                         | 1 Unit/kg<br>(37.5 Units)                                | 2 Units/kg<br>(75 Units)                                  | 2                            |
| Tibialis Posterior             | 1 Unit/kg<br>(37.5 Units)                                | 2 Units/kg<br>(75 Units)                                  | 2                            |

\* did not exceed a total dose of 150 Units

\*\* did not exceed a total dose of 300 Units

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 Clinical Global Impression of Overall Change by Physician (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 (-4=very marked worsening to +4=very marked improvement).

Statistically significant differences between BOTOX and placebo were demonstrated for the MAS and CGI for the 8 Units/kg dose only (see Table 42).

Table 42: Co-Primary Efficacy Endpoints Results in Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population)

|  | BOTOX<br>4 Units/kg<br>(N=125) | BOTOX<br>8 Units/kg<br>(N=127) | Placebo<br>(N=129) |
|--|--------------------------------|--------------------------------|--------------------|
| <b>Mean Change from Baseline in Plantar Flexors on the modified Ashworth Scale</b> |                                |                                |                    |
| Week 4 and 6 Average   | -1.01**                        | -1.06*                         | -0.80              |
| <b>Mean Clinical Global Impression Score</b>                                       |                                |                                |                    |
| Week 4 and 6 Average   | 1.49                           | 1.65*                          | 1.36               |

\* Significantly different from placebo (p<0.05)

\*\* Nominal p value <0.05

Compared to placebo, improvements in mean change from baseline for the MAS, and mean CGI score for lower limb spasticity were observed at timepoints up to Week 12 for BOTOX-treated patients (see Figure 17 and Figure 18).

Figure 17: Modified Ashworth Scale Ankle Score for Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) – Mean Change from Baseline by Visit

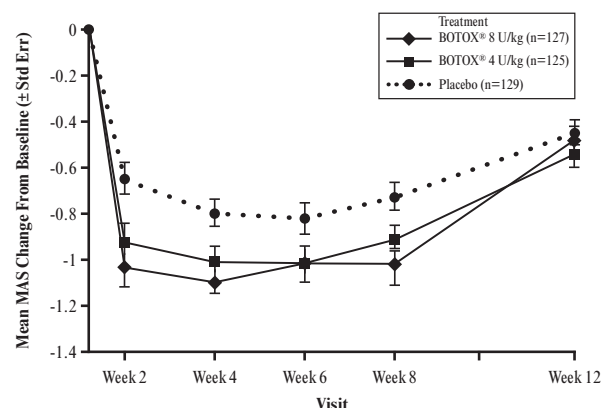
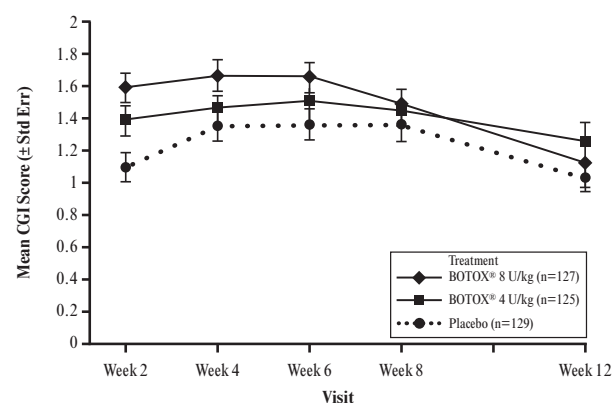


Figure 18: Clinical Global Impression of Overall Change for Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) – Mean Scores by Visit



#### 14.6 Cervical Dystonia

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

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from -4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 43.

Table 43: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

|   | Placebo<br>(N=82) | BOTOX<br>(N=88) | 95% CI on<br>Difference      |
|---|-------------------|-----------------|------------------------------|
| <b>Baseline CDSS</b>  | 9.3               | 9.2             |                              |
| <b>Change in CDSS at Week 6</b>                                       | -0.3              | -1.3            | (-2.3, 0.3) <sup>[a,b]</sup> |
| <b>% Patients with Any Improvement on Physician Global Assessment</b> | 31%               | 51%             | (5%, 34%) <sup>[a]</sup>     |
| <b>Pain Intensity Baseline</b>  | 1.8               | 1.8             |                              |
| <b>Change in Pain Intensity at Week 6</b>                             | -0.1              | -0.4            | (-0.7, -0.2) <sup>[d]</sup>  |
| <b>Pain Frequency Baseline</b>  | 1.9               | 1.8             |                              |
| <b>Change in Pain Frequency at Week 6</b>                             | -0.0              | -0.3            | (-0.5, -0.0) <sup>[d]</sup>  |

<sup>[a]</sup> Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.

<sup>[b]</sup> 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.

<sup>[d]</sup> 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 44. The total dose and muscles selected were tailored to meet individual patient needs.

**Table 44: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles**

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

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

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

**14.7 Primary Axillary Hyperhidrosis**

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = “underarm sweating is never noticeable and never interferes with my daily activities”; to 4 = “underarm sweating is intolerable and always interferes with my daily activities”. A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

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

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

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group (p<0.001), but was not significantly different between the two BOTOX doses (see Table 45).

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

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

**Table 45: Study 1 - Study Outcomes**

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

<sup>a</sup> 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.

**14.8 Blepharospasm**

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

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

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

**14.9 Strabismus**

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

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**16.1 How Supplied**

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried powder supplied in a single-dose vial in the following sizes:  
100 Units NDC 0023-1145-01  
200 Units NDC 0023-3921-02

The top and bottom flaps of the BOTOX cartons have a tamper-evident seal that contains a translucent silver Allergan logo and the BOTOX vial labels have a holographic film that contains the name “Allergan” within rainbow colored horizontal lines (rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source to see the hologram). (Note: the holographic film on the label is absent in the date/lot area.) Each BOTOX vial label and carton also contains the U.S. License number: 1145 [see Dosage and Administration (2.1)].

Do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time if the labeling is not described as above.

**16.2 Storage and Handling**

Unopened vials of BOTOX should be stored in a refrigerator between 2° to 8°C (36° to 46°F) for up to 36 months. Do not use after the expiration date on the vial. Reconstituted BOTOX may be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use [see Dosage and Administration (2.2)].

**17 PATIENT COUNSELING INFORMATION**

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

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms  
Advise patients or their caretaker(s) 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 (5.1, 5.6)].

Ability to Operate Machinery or Vehicles  
Advise patients or their caretaker(s) 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.

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v6.0USPI1145



**MEDICATION GUIDE**  
**BOTOX®**  
**BOTOX® Cosmetic**  
**(Boe-tox)**  
**(onabotulinumtoxinA)**  
**for Injection**

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

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

- **Problems breathing or swallowing**
- **Spread of toxin effects**

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

- **Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.
  - People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
  - Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
  - loss of strength and muscle weakness all over the body
  - double vision, blurred vision and drooping eyelids
  - hoarseness or change or loss of voice (dysphonia)
  - trouble saying words clearly (dysarthria)
  - loss of bladder control
  - trouble breathing
  - trouble swallowing

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

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

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, crow's feet lines, and/or forehead 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 people 2 years of age and older with spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

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

**BOTOX Cosmetic** is a prescription medicine for adults that is injected into muscles and used for a short period of time (temporary) to improve the look of:

- moderate to severe frown lines between the eyebrows (glabellar lines)
- moderate to severe crow's feet lines
- moderate to severe forehead lines

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

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

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 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
- 2 years of age for treatment of spasticity

**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 severe sweating anywhere other than your armpits.

It is not known if **BOTOX Cosmetic** is safe and effective for use more than 1 time every 3 months.

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

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

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc*®, *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 receiving BOTOX or BOTOX Cosmetic?**

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

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See “What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?”

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

**Tell your doctor about all the medicines you take**, including prescription and over-the-counter medicines, vitamins and herbal supplements. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

#### **Especially tell your doctor if you:**

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*® (rimabotulinumtoxinB), *Dysport*® (abobotulinumtoxinA), or *Xeomin*® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)

**Ask your doctor if you are not sure if your medicine is one that is listed above.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

#### **How will I receive BOTOX or BOTOX Cosmetic?**

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

#### **What should I avoid while receiving BOTOX or BOTOX Cosmetic?**

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

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

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

#### **Other side effects of BOTOX and BOTOX Cosmetic include:**

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- drooping eyebrows
- urinary tract infection in people being treated for urinary incontinence
- painful urination in people being treated for urinary incontinence
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.
- upper respiratory tract infection

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **General information about BOTOX and BOTOX Cosmetic:**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for healthcare professionals.

#### **What are the ingredients in BOTOX and BOTOX Cosmetic?**

Active ingredient: onabotulinumtoxin A

Inactive ingredients: human albumin and sodium chloride

Manufactured by: Allergan Pharmaceuticals Ireland  
a subsidiary of: Allergan, Inc.

U.S. License Number 1145

Distributed by: Allergan USA, Inc.

Madison, NJ 07940

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