Injection Workbook for Chronic Migraine
Guidance for identifying BOTOX® patients, the injection procedure, and setting up your practice

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).

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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

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

This workbook is designed to help you learn and apply the proven BOTOX® Injection Paradigm. It also contains information to help injectors identify appropriate BOTOX® candidates, understand procedure-related anatomy, manage patient expectations, and integrate the procedure into the practice.

Reference material accompanying this workbook:

Reconstitution pocket guide

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

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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“PREEMPT® = Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Serious Adverse Reactions With Unapproved Use

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

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

Practical clinical criteria for Chronic Migraine diagnosis\(^1,2\)

- **15** or more headache days per month
- **8** or more headache days are migraine days

*With or without medication overuse\(^2\)*

Focus on headache days vs migraine attacks

- Not all days need to be associated with migraine\(^2\)
- Days when headaches were successfully treated with migraine-specific acute medications (eg, triptans) are also considered headache days\(^1\)
- Ask about headache-free days if patient cannot recall number of actual headache days

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.

Revisit appropriate Chronic Migraine patients’ treatment plans with BOTOX® in mind

A history of preventive use\(^5\)

Considerations when evaluating treatment plans

Prevention may be an important part of a Chronic Migraine management plan. Aside from ensuring adequate prevention, a management plan may include optimizing acute medication use/limiting medication overuse, addressing comorbid conditions, and adjusting patient lifestyles (eg, diet, exercise, curbing caffeine overuse).\(^1,2\)

Treatment planning begins with a thorough history, which can include inquiry around these topics:

- Is the patient using more acute medications than recommended?
- Is the patient responding appropriately to acute medications?
- Is the patient meeting treatment goals?
- Has the patient followed the prescribed preventive regimen?
- Are there contraindications to some treatment options?

Chronic Migraine patients have tried **3.9** preventive treatments on average (n = 493)\(^5\)

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Pre-Existing Neuromuscular Disorders

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

Please see additional Important Safety Information about BOTOX® on following pages.
Identifying BOTOX® candidates (continued)

As part of the evaluation, documenting symptoms for a Chronic Migraine diagnosis is important. When patients can understand the symptoms of their condition, they may feel less frustrated and more open to treatment options.

| Headache frequency and duration | Evaluate both headache days and headache-free days |
| Headache severity | Ask about symptoms and intensity, which may shed light on headache severity |
| Headache impact | Uncover how headache affects daily activities to avoid a patient minimizing symptoms |

Greater disability correlates with headache frequency

Patients with Chronic Migraine are significantly more likely to be severely disabled than those with episodic migraine (64.3% vs 43.2% Migraine Disability Assessment [MIDAS] grade IV).

PREEMPT injection protocol overview

PREEMPT injection protocol is based on 10 years of study to assess patient type, muscle selection, dose, and treatment interval.

- **PROVEN DOSE**: 155 Units
- **PROVEN SCHEDULE**: Re-treatment every 12 weeks
- **PROVEN SITES**: 31 sites across 7 specific head and neck muscle areas

Summary of dose by area

<table>
<thead>
<tr>
<th>MUSCLE AREA</th>
<th>RECOMMENDED DOSE/NUMBER OF SITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrugator</td>
<td>10 Units divided between 2 sites</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 Units in 1 site</td>
</tr>
<tr>
<td>Frontalis</td>
<td>20 Units divided between 4 sites</td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 Units divided between 8 sites</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 Units divided between 6 sites</td>
</tr>
<tr>
<td>Cervical paraspinal</td>
<td>20 Units divided between 4 sites</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 Units divided between 6 sites</td>
</tr>
<tr>
<td><strong>TOTAL DOSE</strong></td>
<td>155 Units* divided between 31 sites</td>
</tr>
</tbody>
</table>

*Document and discard the 45-Unit wastage.

The following section provides a step-by-step overview of the injection 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)

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).

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

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)
- Consider injecting in the most superficial aspect of the muscle
- Evaluate the anatomy, including relevant function and the effects of treatment on these muscles (e.g., weakening)
- 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 delivery point of the medication

BEFORE INJECTION

- Examine the patient to identify unique anatomy and any muscle weakness or pain/tenderness
  - Visually inspect the muscle
  - Ask the patient to activate the muscle
  - Palpate the muscle
- 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)

ADVERSE REACTIONS

The following adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning); Hypersensitivity Reactions (see Contraindications and Warnings and Precautions); Dysphagia and Breathing Difficulties (see Warnings and Precautions).

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 paresthesia (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.

DURING INJECTION

- Inject on 1 side first for bilateral injections, then proceed to the other side and repeat at all the specified sites
- 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

Example of procerus injection. Note the angle used to avoid the periosteum and target the muscle (Figure 1).

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS (continued)

Post Marketing Experience

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

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

Anatomy of the face and head

This section will highlight muscle area anatomy to provide additional context for the anterior injection sites.

**IMPORTANT SAFETY INFORMATION (continued)**

**DRUG INTERACTIONS**

Co-administration of BOTOX® and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX®.

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

**Temporals**

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.17

**Procerus**

Originates from the aponeurotic fascia of the nose and inserts into the glabellar skin.17

**Corrugator**

Attaches to the nasal-frontal bone medially and the skin of the eyebrow laterally.17,18

**Frontalis**

Originates from the epicranial aponeurosis, and attaches distally to the skin of the forehead and eyebrow.17

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.

**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).

**Important Limitations**

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

Please see Important Safety Information including Boxed Warning about BOTOX® on following pages.
**Anterior injections (continued)**

**Functional anatomy**

This section will highlight the functional anatomy of each anterior injection site, which may be important to consider when injecting.

The **frontalis muscle** is a brow elevator, pulling the brow upward.\(^\text{17}\) Weakening of this muscle may result in brow ptosis.

Activating the frontalis creates transverse lines on the forehead (Figure 2).\(^\text{17}\)

The **corrugator muscle** is a brow depressor, pulling the brow downward.\(^\text{17}\) Weakening of this muscle may elevate the brow.

Activating the corrugator creates vertical lines between the brow (Figure 3).\(^\text{17}\)

**Functional anatomy (continued)**

The **procerus muscle** draws down the medial aspect of the brow.\(^\text{17}\)

Activating the procerus creates a transverse ridge over the nose (Figure 4).\(^\text{17}\)

The **temporalis** is a masticatory muscle. Clenching the teeth activates the temporalis and can help localize the muscle (Figure 5).\(^\text{17}\)

\(^\text{17}\) This is a hypothetical patient.

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**IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING**

**WARNING: DISTANT SPREAD OF TOXIN EFFECT**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

**Lack of Interchangeability Between Botulinum Toxin Products**

The potency Units of BOTOX\(^\text{®}\) 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\(^\text{®}\) cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

**Spread of Toxin Effect**

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX\(^\text{®}\) for chronic migraine at the labeled dose have been reported.

**IMPORTANT SAFETY INFORMATION (continued)**

**Please see additional Important Safety Information about BOTOX\(^\text{®}\) on following pages.**
**Standard corrugator PREEMPT protocol**

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

**Injection site**
- About 1.5 cm (= 1 fingerbreadth) above the medial inferior edge of the superior orbital rim (bony landmark). This may vary based on individual anatomy

**Medial superior edge of the corrugator muscle**

**Corrugator injection sites**

*Muscles and anatomical structures shown for anatomical reference only.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

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

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

**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 between the thumb and index finger (Figure 6)
- 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 6)
- 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.
**Standard procerus PREEMPT protocol**

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

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

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**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.

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

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

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**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 90º to deliver medication into the procerus and not a nearby muscle (eg, frontalis) (Figure 7)
- 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

**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 frontalis PREEMPT protocol

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

Medial injection site
- 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 (~1 fingerbreadth) above the corrugator injection site. This may vary based on individual anatomy

Lateral injection site
- Lateral injections are parallel, lining up with the lateral limbus of the cornea, and at least 1.5 cm (~1 fingerbreadth) lateral to the medial injection site (Figure 8). This may vary based on individual anatomy

Additional factors to consider prior to injection
- Angle the needle superiorly at 45º (Figure 9)
- Frontalis muscles are thin, so inject in 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
- Weakening the frontalis may exacerbate preexisting brow ptosis; counsel patients with this condition accordingly (see page 32)
- 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)

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.

Please see additional Important Safety Information about BOTOX® on following pages.
Standard temporalis PREEMPT protocol*

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

Injection site
- Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm (~2 fingerbreadths)

Injection site
- Move about 1.5 cm to 3 cm (~1-2 fingerbreadths) up from the first injection, still in line with the tragus of the ear

Injection site
- Move about 1.5 cm to 3 cm (~1-2 fingerbreadths) forward, toward the face, from the first and second injections. Make the third injection halfway vertically between injection sites 1 and 2

Injection site
- Find the tragus of the ear and move your finger vertically up the side of the head about 3 cm (~2 fingerbreadths)

*Muscles and anatomical structures shown for anatomical reference only.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS
The following adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning); Hypersensitivity Reactions (see Contraindications and Warnings and Precautions); Dysphagia and Breathing Difficulties (see Warnings and Precautions).

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

Muscles of the neck and posterior head

This section will highlight muscle area and functional anatomy for each posterior injection site, which may be important to consider when injecting.

**Occipitalis**—Originates at the highest nuchal line and inserts into the epicranial aponeurosis, which is attached to the frontalis.17

**Cervical paraspinal muscles** should be considered a group (including the splenius capitis and semispinalis capitis) running deep alongside the cervical spine.17

**Trapezius**—A flat, triangular muscle situated over the back of the neck and upper thorax.17

*Muscles and anatomical structures shown for anatomical reference only.

**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 2%), 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.

**Functional anatomy**

One function of the **occipitalis** is as an anchor for the frontalis.17

**Cervical paraspinal muscles** stabilize and allow for movement of the head and cervical spine (Figure 11).17

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 12).17

† This is a hypothetical patient.
Standard occipitalis PREEMPT protocol*

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

**Injection site 1**
- Palpate the occipital protuberance and find the most posterior point (inion) in the midline (Figure 13)
- Locate the tip of the mastoid process behind the ear (Figure 13)
- 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 2**
- Measure a diagonal fingerbreadth up and out toward the superior helix of the ear (see diagram on page 20) for the second muscle area for injection (eg, at the 10 o’clock position for the left injection)

**Injection site 3**
- Measure a diagonal fingerbreadth up and medial for the third muscle area for injection (eg, at the 2 o’clock position for the left injection)

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*Muscles and anatomical structures shown for anatomical reference only.

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**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 14)
- Inject at 45º, angling the needle upward and away from the neck (Figure 14)
- 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)**

**ADVERSE REACTIONS (continued)**

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

Please see additional Important Safety Information about BOTOX® on following pages.
Standard cervical paraspinal PREEMPT protocol*

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

Injection site 1
• Measure about 1 cm left of the midline of the cervical spine and about 3 cm (= 2 fingerbreadths) inferior to the lower border of the occipital protuberance.

Injection site 2
• Measure about 1.5 cm (= 1 fingerbreadth) diagonally up at a 45º angle toward the helix of the ear (see diagram on page 20) from the first injection site.

IMPORTANT SAFETY INFORMATION (continued)

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

Please see additional Important Safety Information about BOTOX® on following pages.
Standard trapezius PREEMPT protocol

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

Injection site 1
- Divide the upper portion of the trapezius muscle in half, from the inflection point of the neck (necklace line) to the acromion
- The first injection is located at this midpoint

Injection site 2
- Split the difference between injection 1 and the acromion

Injection site 3
- Split the difference between injection 1 and the necklace line

*Muscles and anatomical structures shown for anatomical reference only.

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS (continued)
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.

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 16)
- Inject the supraclavicular portion of the muscle, lateral to the neckline and medial to the deltoid/acromion joint (Figure 16)
- 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.

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).

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

Please see Important Safety Information including Boxed Warning about BOTOX® on following pages.
Adverse events observed during PREEMPT pivotal trials

Adverse reactions ≥ 5% in Chronic Migraine clinical trials were headache and neck pain (n = 687).

<table>
<thead>
<tr>
<th>Adverse Reactions by Body System</th>
<th>BOTOX® 155 Units to 195 Units (n = 687)</th>
<th>Placebo (n = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32 (5%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>26 (4%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (4%)</td>
<td>2 (&lt; 1%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (3%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective-tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (9%)</td>
<td>19 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (4%)</td>
<td>2 (&lt; 1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (3%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>23 (3%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (2%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

Discontinuation rates due to adverse events

Oberved treatment-related adverse events were typically mild to moderate in severity.

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Facial paresis</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION (continued)**

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

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.
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

**Preexamination of the brow**

*What to look for:* Inspect for excessive soft tissue resting near the upper lid of the eye and lid drooping (Figure 17).

**Preexamination 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 her 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.

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Serious Adverse Reactions With Unapproved Use**

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

**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.
Patient assessment before injection (continued)

Preexamination of the neck

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

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).

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

Pre-Existing Neuromuscular Disorders

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

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.
Managing patient expectations

BEFORE INJECTION
• Discuss goals of preventive vs acute therapy
• Confirm a commitment to the entire treatment process
  – Reinforce treatment as an ongoing plan, not a single procedure
  – Communicate that treatment is every 12 weeks, with efficacy evaluated at 24 weeks in clinical trials\(^1\)
• Assess the patient for preexisting conditions and counsel accordingly
• Talk about any concerns related to needles and discomfort
  – Providers may consider topical anesthetic on appropriate areas (eg, frontalis)
  – Explain how the needle insertion may feel (eg, like a small pinprick sensation)

DURING INJECTION
• Talk to patients as you perform injections
• Ensure the patient is comfortable
  – Switch needles frequently to avoid pain caused by dull needles

AFTER INJECTION
• Reinforce the treatment schedule
  – Preschedule patients to avoid missing treatments every 12 weeks
• Tell patients it may take time to notice a response
  – Efficacy will be assessed at 24 weeks\(^1\)
• Plan for follow-up at 4 to 6 weeks to monitor progress and check for adverse events

Tips to efficiently adopt BOTOX\(^{\circ}\) in the office

Office staff and processes:
• Assign staff to specific roles
  ✓ Roles include ordering and submitting insurance verifications, prior authorizations, and claims
• Have a process to identify Chronic Migraine patients
  ✓ Use a screener and symptom assessment tool to document symptoms and medication history
• Use a system to track and schedule recurring treatment
  ✓ Ensure patients receive treatment every 12 weeks
  ✓ Send reminders 1 to 2 weeks before the appointment
• Set up BOTOX\(^{\circ}\) Clinic Days from the beginning
  ✓ Improve patient flow 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
  ✓ Train nursing staff to reconstitute and prepare syringes of BOTOX\(^{\circ}\)

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS
The following adverse reactions to BOTOX\(^{\circ}\) for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning); Hypersensitivity Reactions (see Contraindications and Warnings and Precautions); Dysphagia and Breathing Difficulties (see Warnings and Precautions).

Chronic Migraine
The most frequently reported adverse reactions following injection of BOTOX\(^{\circ}\) 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\(^{\circ}\) 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\(^{\circ}\) on following pages.
Tips to efficiently adopt BOTOX® in the office (continued)

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

- Medication history
- Defined medical necessity
- Services provided
- BOTOX® administration details (sites, Units, schedule)
- Clinical effectiveness and/or outcomes of BOTOX® therapy

Allergan is here to help
Ask about working with a Neuroscience Business Practice Specialist (NBPS) for in-person advice on reimbursement. There should be no financial barriers to patients accessing BOTOX® treatment.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

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

Your patients may already meet their insurance policy requirements for BOTOX®

Majority of lives require trial of 2 or fewer oral preventives

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or fewer</td>
<td>77.5%</td>
</tr>
<tr>
<td>3 or more</td>
<td>9.7%</td>
</tr>
<tr>
<td>N/A</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

Chronic Migraine patients have tried 3.9 preventive treatments on average (n = 493)

*As of Q2 2015.

Understanding oral preventive trial requirements
Some factors considered when determining adequate treatment trial include:

- 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

Check with individual payer policies for specific treatment trial requirements.

IMPORTANT SAFETY INFORMATION (continued)
DRUG INTERACTIONS

Co-administration of BOTOX® and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX®.

Please see accompanying full Prescribing Information including Boxed Warning and Medication Guide.
Resources available to your patients

Ask your Allergan representative for more information about these resources or visit BotoxAcademy.com to download or learn more.

Patient education and financial assistance

BOTOX® for Chronic Migraine patient brochure
Introduction to treatment for patients considering BOTOX® as their next step. Also available in Spanish.

Getting Started With BOTOX® brochure
Information to help patients understand what to expect when starting treatment.

Pathways Prevention
Patient support program
Patients receive treatment reminders and healthy-living tips from the editors of Prevention® magazine. Patients register at BOTOXChronicMigraine.com.

Co-pay savings for commercially insured patients
2 out of 3 new patients pay nothing out-of-pocket when they qualify for the $250 Savings Program.Visit AccessBSC.com for more information or to help your patients enroll.

Assistance for underinsured or uninsured patients
The BOTOX PATIENT ASSISTANCE® PROGRAM can help qualified patients with the cost of BOTOX®.
Visit BOTOXReimbursementSolutions.com to download an application.

*Limitations apply. Please visit AccessBSC.com for full eligibility details.
*96% of patients pay ≤ $250 out-of-pocket (OOP) before applying the Savings Program, meaning the $250 Savings Program covers the OOP costs.
The median OOP cost for all patients is $180 before applying the Savings Program.
*Current BOTOX® patients can receive up to $100 per treatment.

Resources available to injectors and the office

Office resources

Treatment record pad
Helps record treatment information (sites, dose) for the injector and/or office staff.

Neuroscience Business Practice Specialists
These experts in BOTOX® reimbursement processes can walk you through specific payer policies, as well as provide advice on operational efficiencies.

Peer-to-peer training
Preceptorships, proctorships, and advanced group workshops are available to help improve your technique.

Online videos and education at BOTOXAcademy.com
Register for ongoing education and to download tools for your office.

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 or more hours each day in people 18 years or older).

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

IMPORTANT SAFETY INFORMATION (continued)

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

Please see Important Safety Information including Boxed Warning about BOTOX® throughout this brochure.
Please see Important Safety Information including Boxed Warning about BOTOX® throughout this brochure.
References:
1. BOTOX® Prescribing Information, August 2015.
24. BOTOX® for injection is indicated for the prophylaxis of headaches in adult patients with chronic migraine. *marked owned by Allergan, Inc. **Prevention is a registered trademark of Rodale Inc. **BOTOX® for injection is a registered trademark of Allergan, Inc. ***AccessBSC.com BOTOX® Reimbursement Solutions.com 1-800-44-BOTOX® 152490
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.
BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use
Initial U.S. Approval: 1989

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

RECENT MAJOR CHANGES
• Indications and Usage, Upper Limb Spasticity (1.3) 04/2015
• Dosage and Administration (2.1, 2.5) 04/2015
• Warnings and Precautions, Serious Adverse Reactions with Unapproved Use (5.3) 08/2015

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 upper limb spasticity in adult patients (1.3)
• Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
• Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
• Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)
• Treatment of strabismus in patients ≥12 years of age (1.6)

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

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

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

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS:
WARNING: Distant Spread of Toxin Effect
1 INDICATIONS AND USAGE
  1.1 Bladder Dysfunction
  1.2 Chronic Migraine
  1.3 Upper Limb Spasticity
  1.4 Cervical Dystonia
  1.5 Primary Axillary Hyperhidrosis
  1.6 Blepharospasm and Strabismus

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

3 CONTRAINDICATIONS

4 WARNINGS AND PRECAUTIONS

5 ADVERSE REACTIONS

6 USE IN SPECIFIC POPULATIONS

7 DRUG INTERACTIONS

8 DRUG CONSIDERATIONS

9 DOSAGE FORMS AND STRENGTHS

10 RECENT MAJOR CHANGES

11 INDICATIONS AND USAGE

12 ADVERSE REACTIONS

13 WARNINGS AND PRECAUTIONS

14 CONTRAINDICATIONS

15 INSTRUCTIONS FOR SAFE USE

16 PREPARATION AND DILUTION TECHNIQUE

17 PATIENT COUNSELING INFORMATION

18 MEDICATION GUIDE
1.4 Cervical Dystonia

Safety and effectiveness of BOTOX have not been established for the treatment of other (e.g., SCI, MS) 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 underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses. [See Warnings and Precautions (5.2)]

1.5 Primary Auxillary Hyperhidrosis

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

Important limitations

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharospasm 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 an underlying disease.

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).

Important limitations

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

1.3 Upper Limb Spasticity

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

Important limitations

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

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.
Dilution Instructions for BOTOX Vials (100 Units and 200 Units)**

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

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

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

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

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

### 2.3 Bladder Dysfunction

**General**

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

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

Appropriate caution should be exercised when performing a cystoscopy.

**Overactive Bladder**

An intravesical instillation of diluted local anesthetic with or without sedation 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.

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 needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 0.1 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 saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

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

### 2.4 Chronic Migraine

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

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

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

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

2.5 Upper Limb Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient’s response to previous treatment, or adverse event history with BOTOX. In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 3 and Figure 2) at a given treatment session.

Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity

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

2.7 Primary Axillary Hyperhidrosis

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

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

Instructions for the Minor’s Iodine-Starch Test Procedure:
- Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.
- Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 3.

Figure 3: Injection Pattern for Primary Axillary Hyperhidrosis

Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain superficial, which 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 more 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 hyperhidrosis in a 30-day period should not exceed 200 Units.

2.8 Blepharospasm

For blepharospasm, reconstituted BOTOX is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units-2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Echymosis 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 more 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 hyperhidrosis in a 30-day period should not exceed 200 Units.

2.9 Strabismus

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

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection. The volume of BOTOX injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.
The initial listed doses of the reconstituted BOTOX [see Dosage and Administration (2.2)] typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

Initial doses in Units
Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

Subsequent doses for residual or recurrent strabismus
- It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- The maximum recommended dose as a single injection for any one muscle is 25 Units. The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL [see Table 1].

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

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin
BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation [see Warnings and Precautions (5.4)].

4.2 Infection at the Injection Site(s)
BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

4.3 Urinary Tract Infection or Urinary Retention
Intradetrusor injection of BOTOX is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection. Intradetrusor injection of BOTOX is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200 mL, who are not routinely performing clean intermittent self-catheterization (CIC).

5 WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

5.5 Pre-Existing Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX [see Adverse Reactions (6.1)].

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

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

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

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

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

Patients with unapproved respiratory status treated with BOTOX for upper limb spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients with stable reduced pulmonary function (defined as FEV1, 40-80% of predicted value and VC < 0.75), the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo [see Table 4].

Table 4: Event rate per patient treatment cycle among patients with reduced lung function at the labeled doses of BOTOX or placebo

<table>
<thead>
<tr>
<th>Neurologic Condition</th>
<th>BOTOX 360 Units</th>
<th>BOTOX 240 Units</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15%</td>
<td>≥20%</td>
<td>≥15%</td>
<td>≥20%</td>
</tr>
<tr>
<td>Week 1</td>
<td>4%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Week 12</td>
<td>10%</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Differences from placebo were not statistically significant.

In patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo [see Warnings and Precautions (5.10)].
In an ongoing double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity \( \geq 15\% \) or ≥20\% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 5).

### Table 5: Number and percent of patients experiencing at least a 15\% or 20\% decrease in FVC from baseline at Week 2, 6, 12 post-injection with BOTOX or placebo

| Timepoint       | BOTOX 200 Units | Placebo  
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \geq 15% )</td>
<td>( \geq 20% )</td>
</tr>
<tr>
<td>Week 2</td>
<td>0/12 (0%)</td>
<td>0/12 (0%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>2/11 (18%)</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0/11 (0%)</td>
<td>0/11 (0%)</td>
</tr>
</tbody>
</table>

### 5.8 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

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

### 5.9 Retrolublar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of BOTOX for the treatment of strabismus, retrolublar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decomprom the orbit be accessible.

### 5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX (3\% at 251 Units-360 Units total dose), compared to placebo (1\%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11\% at 360 Units total dose; 8\% at 240 Units total dose) compared to placebo (6\%).

### 5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition

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

### 5.12 Urinary Tract Infections in Patients with Overactive Bladder

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

### 5.13 Urinary Retention in Patients Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

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

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

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

### Table 6: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials in OAB

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

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 7.

### Table 7: Proportion of Patients Experiencing Urinary Retention following an injection in double-blind, placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units (N=81)</td>
<td>Placebo (N=89)</td>
</tr>
<tr>
<td>BOTOX 100 Units (N=526)</td>
<td>Placebo (N=516)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>12.3% (n=10)</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

### 5.14 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

### 6 ADVERSE REACTIONS

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

- Spread of Toxin Effects [see Warnings and Precautions (5.2)]
- Hypersensitivity [see Contraindications (4.1) and Warnings and Precautions (5.4)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity [see Warnings and Precautions (5.10)]
- Urinary Retention in Patients Treated for Bladder Dysfunction [see Warnings and Precautions (5.13)]
6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse reactions observed with the use of BOTOX Cosmetic also have the potential to be observed with the use of BOTOX.

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

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

Overactive Bladder

Table 10 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 10: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Often than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-blind, Placebo-controlled Clinical Trials in Patients with OAB

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

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

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

Table 11: Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Placebo (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units (N=81)</td>
<td>25 (31%)</td>
</tr>
<tr>
<td>Placebo (N=516)</td>
<td>8 (12%)</td>
</tr>
</tbody>
</table>

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

Detrusor Overactivity associated with a Neurologic Condition

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 200 Units (N=262)</th>
<th>Placebo (N=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>64 (24%)</td>
<td>47 (17%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>45 (17%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>10 (4%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

Chronic Migraine

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

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 13.

Table 13: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX ≥155 Units (N=687)</th>
<th>Placebo (N=692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32 (5%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>26 (4%)</td>
<td>18 (3%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (3%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (9%)</td>
<td>19 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (3%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (2%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>23 (3%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (2%)</td>
<td>7 (1%)</td>
</tr>
</tbody>
</table>

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

Upper Limb Spasticity

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

Table 14: Adverse Reactions Reported by ≥2% of BOTOX Treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-blind, Placebo-controlled Clinical Trials

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

Twenty two adult patients, enrolled in double-blind placebo controlled studies, received 400 Units or higher of BOTOX for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX or higher for four consecutive treatments over approximately one year for treatment of upper limb spasticity. The type and frequency of adverse reactions observed in patients treated with 400 Units of BOTOX were similar to those reported in patients treated for upper limb spasticity with 360 Units of BOTOX.
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 (5.2, 5.6)]. The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea [see Warnings and Precautions (5.2, 5.6)]. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms [see Warnings and Precautions (5.6)].

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

Primary Axillary Hyperhidrosis
The most frequently reported adverse reactions (3-10% of adult patients) following injection of BOTOX in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, 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 paresthesia (21%), superficial punctate keratitis (6%), and eye dryness (6%). Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

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

Strabismus
Extracocular muscles adjacent to the injection site can be affected, causing vertical deviation, exotropia 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. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin.

In a long-term, open-label study evaluating 326 cervical dystonia patients treated for an average of 8 treatment sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to BOTOX therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to BOTOX therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), no patients among 406 migraine patients, no patients among 615 overactive bladder patients, and no patients among 475 detrusor overactivity associated with a neurologic condition patients with analyzed specimens developed the presence of neutralizing antibodies.

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

6.3 Post-Marketing Experience
The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; deneveration/muscle atrophy; diarrhea; hyperhidrosis; hypoacusis; hypoesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermographia purpuraform, and purpuraform erosion; strabismus; tinnitus; and visual disturbances.

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

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

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

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

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

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. BOTOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats twice during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 0.7 times the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

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

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 3 times the average high human dose based on Units/kg.

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

8.4 Pediatric Use
Bladder Dysfunction
Safety and effectiveness in patients below the age of 18 years have not been established.

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

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

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

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

8.5 Geriatric Use

Overall, with the exception of Overactive Bladder (see below), clinical studies of BOTOX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There was no evidence of geriatric use above the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 15). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

Table 15. Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>&lt;65 Years</th>
<th>65 to 74 Years</th>
<th>≥75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units</td>
<td>73 (21%)</td>
<td>23 (7%)</td>
<td>51 (30%)</td>
</tr>
<tr>
<td>(N=344)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>51 (30%)</td>
<td>20 (13%)</td>
<td>36 (38%)</td>
</tr>
<tr>
<td>BOTOX 100 Units</td>
<td>16 (19%)</td>
<td>14 (8%)</td>
<td>8 (9%)</td>
</tr>
<tr>
<td>(N=169)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>16 (19%)</td>
<td>8 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>BOTOX 100 Units</td>
<td>23 (7%)</td>
<td>51 (30%)</td>
<td>36 (38%)</td>
</tr>
<tr>
<td>(N=94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>16 (19%)</td>
<td>8 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>BOTOX 100 Units</td>
<td>16 (19%)</td>
<td>8 (9%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>(N=86)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

10 OVERDOSAGE

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

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

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory musculature 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 or a gastrostomy tube. Ventilation and mechanical ventilation, in addition to other general supportive care.

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

11 DESCRIPTION

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

Following intradermoeular injection, BOTOX affects the effector pathways of detrusor activity via inhibition of acetylcholine release.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses; 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

13.2 Animal Toxicology

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

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 16 and 17, and Figures 4 and 5.
Table 16: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units (N=275)</th>
<th>Placebo (N=272)</th>
<th>Treatment Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Frequency of Urinary Incontinence Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-2.6</td>
<td>-1.0</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6</td>
<td>-2.8</td>
<td>-1.0</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 12**</td>
<td>-2.5</td>
<td>-0.9</td>
<td>-1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-2.1, -1.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Daily Frequency of Micturition Episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>12.0</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12**</td>
<td>-1.9</td>
<td>-0.9</td>
<td>-1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-1.5, -0.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Volume Voided per Micturition</strong> (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>156</td>
<td>161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12**</td>
<td>38</td>
<td>8</td>
<td>30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(17, 43)</td>
<td></td>
</tr>
</tbody>
</table>

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

Table 17: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

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

* LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and 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 time point
a Primary variable
b Secondary variable

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

14.2 Detrusor Overactivity associated with a Neurologic Condition

Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241). In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 18 and 19, and Figures 6 and 7.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.
Table 18: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) Study NDO-1

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
<th>Treatment Difference*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence Episodes**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>134</td>
<td>146</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.3</td>
<td>28.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-15.3</td>
<td>-10.0</td>
<td>-5.3</td>
<td>—</td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-19.9</td>
<td>-10.6</td>
<td>-9.2 (-13.1, -5.3)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-19.8</td>
<td>-8.8</td>
<td>-11.0</td>
<td>—</td>
</tr>
<tr>
<td><strong>Maximum Cystometric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capacity (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>123</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>253.8</td>
<td>259.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>135.9</td>
<td>12.1</td>
<td>123.9 (89.1, 158.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>during First Involuntary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detrusor Contraction (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>41</td>
<td>103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>63.1</td>
<td>57.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-28.1</td>
<td>-3.7</td>
<td>-24.4</td>
<td>—</td>
</tr>
</tbody>
</table>

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

** Primary timepoint

*a Primary endpoint

*b Secondary endpoint

Table 19: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-2

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
<th>Treatment Difference*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incontinence Episodes**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>91</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.7</td>
<td>36.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 2</td>
<td>-18.0</td>
<td>-7.9</td>
<td>-10.1</td>
<td>—</td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-19.6</td>
<td>-10.8</td>
<td>-8.8 (-14.5, -3.0)</td>
<td>p&lt;0.003</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-19.6</td>
<td>-10.7</td>
<td>-8.9</td>
<td>—</td>
</tr>
<tr>
<td><strong>Maximum Cystometric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capacity (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>88</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>239.6</td>
<td>253.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>150.8</td>
<td>2.8</td>
<td>148.0 (101.8, 194.2)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>during First Involuntary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detrusor Contraction (cmH₂O)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>65.6</td>
<td>43.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change* at Week 6**</td>
<td>-28.7</td>
<td>2.1</td>
<td>-30.7</td>
<td>—</td>
</tr>
</tbody>
</table>

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

** Primary timepoint

*a Primary endpoint

*b Secondary endpoint

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

14.3 Chronic Migraine

BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had ≥15 headache days lasting 4 hours or more, with ≥50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 20).

Table 20: Week 24 Key Efficacy Variables for Study 1 and Study 2

<table>
<thead>
<tr>
<th>Efficacy per 28 days</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in frequency of</td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td>headache days</td>
<td>(N=341)</td>
<td>(N=338)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in total</td>
<td>BOTOX</td>
<td>Placebo</td>
</tr>
<tr>
<td>cumulative hours of headache on</td>
<td>(N=341)</td>
<td>(N=338)</td>
</tr>
<tr>
<td>headache days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Significantly different from placebo (p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 8), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 9), compared to placebo-treated patients.
14.4 Upper Limb Spasticity

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

Study 1 included 126 patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 3 weeks post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 21). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 21: Study Medication Dose and Injection Sites in Study 1

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

* injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 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).

Possible scores range from 0 to 4:

1 = Slight increase in muscle tone, giving a ‘catch’ when the limb was moved in flexion or extension (mild)

2 = More marked increase in muscle tone but affected limb is easily flexed (moderate)

3 = Considerable increase in muscle tone - passive movement difficult (severe)

4 = Limb rigid in flexion or extension (very severe).

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 22.

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

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

* Primary endpoint at Week 6
† Secondary endpoints at Week 6
‡ Significantly different from placebo (p < 0.05)
§ BOTOX injected into both the flexor carpi radialis and ulnaris muscles
∥ BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
¶ BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 patients [BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 23).

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX low dose (90 Units)</td>
<td></td>
</tr>
<tr>
<td>BOTOX mid dose (180 Units)</td>
<td></td>
</tr>
<tr>
<td>BOTOX high dose (360 Units)</td>
<td></td>
</tr>
<tr>
<td>Volume (mL) per site</td>
<td>Injection Sites (n)</td>
</tr>
<tr>
<td>Wrist</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>40 Units</td>
</tr>
<tr>
<td>Finger</td>
<td>0.6</td>
</tr>
<tr>
<td>Flexor Digitorum Profundus</td>
<td>30 Units</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>30 Units</td>
</tr>
<tr>
<td>Elbow</td>
<td>0.5</td>
</tr>
<tr>
<td>Biceps Brachii</td>
<td>200 Units</td>
</tr>
</tbody>
</table>

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

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 24.

Table 24: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

<table>
<thead>
<tr>
<th>BOTOX low dose (90 Units) (N=21)</th>
<th>BOTOX mid dose (180 Units) (N=23)</th>
<th>BOTOX high dose (360 Units) (N=21)</th>
<th>Placebo (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale</td>
<td>-1.5* -1.0* -1.5*</td>
<td></td>
<td>-1.0</td>
</tr>
<tr>
<td>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale</td>
<td>-0.5 -0.5 -1.0</td>
<td></td>
<td>-0.5</td>
</tr>
<tr>
<td>Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale</td>
<td>-0.5 -1.0* -0.5*</td>
<td></td>
<td>-0.5</td>
</tr>
<tr>
<td>Median Physician Global Assessment of Response to Treatment</td>
<td>1.0* 1.0* 1.0*</td>
<td></td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Primary endpoint at Week 6
† Secondary endpoints at Week 6
‡ Significantly different from placebo (p < 0.05)
§ p=0.053
∥ Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles
¶ Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
†† Dose of BOTOX injected into biceps brachii muscle
Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 patients [BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)] 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 23).

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 25.

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

<table>
<thead>
<tr>
<th>Study 4</th>
<th>Study 5</th>
<th>Number of Injection Sites for Studies 4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles Injected</td>
<td>BOTOX (Units)</td>
<td>Volume (mL)</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and overall treatment response by Physician Global Assessment at week 6 are presented in Table 27.

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

<table>
<thead>
<tr>
<th>BOTOX (N=86)</th>
<th>Placebo (N=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale</td>
<td>-1.0</td>
</tr>
<tr>
<td>Median Physician Global Assessment of Response to Treatment</td>
<td>2.0</td>
</tr>
</tbody>
</table>

11 Secondary endpoints at Week 6
* Significantly different from placebo (p≤0.05)
† Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles
†† Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
††† Dose of BOTOX injected into biceps brachii muscle

Study 4 included 170 patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 5, patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus muscles. The duration of follow-up in Study 4 and Study 5 was 12 weeks.

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

<table>
<thead>
<tr>
<th>Study 4</th>
<th>Study 5</th>
<th>Number of Injection Sites for Studies 4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscles Injected</td>
<td>BOTOX (Units)</td>
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</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
</tr>
</tbody>
</table>

The primary endpoint at Week 6
††† Significantly different from placebo (p≤0.01)
† BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

14.5 Cervical Dystonia

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

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS 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 29.

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

<table>
<thead>
<tr>
<th>BOTOX low dose (30 Units) (N=14)</th>
<th>Placebo low dose (N=9)</th>
<th>BOTOX high dose (40 Units) (N=45)</th>
<th>Placebo high dose (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>Median Change from Baseline in Clinical Global Impression Score by Physician</td>
<td>1.0</td>
<td>0.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

11† Secondary endpoint at Week 6
11†† Other endpoint at Week 6
* Significantly different from placebo (p≤0.01)
† BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

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

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

** Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
*** These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.
†† Confidence intervals are based on the t-distribution.

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

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 30. The total dose and muscles selected were tailored to meet individual patient needs.
percentages of responders were 91% (219/242) in the BOTOX group and 36% (28/78) in the placebo group. At week 4 post-injection, the response was similar to that observed after the first treatment.

Duration of response was calculated as the number of days between injection and the date of failure. 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, 75 Units and 30-placebo groups respectively. The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group (p<0.001), but was not significantly different between the two BOTOX doses (see Table 31).

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

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of BOTOX (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction in 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).

In study 3, 677 patients with strabismus treated with one or more injections of BOTOX were evaluated in an open label trial. Fifty-five percent of these patients showed at least a 2-grade improvement of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

### 14.8 Strabismus

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

### 14.7 Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of BOTOX at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired. In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks. One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

### Table 30: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

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

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

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

### Table 31: Study 1 - Study Outcomes

<table>
<thead>
<tr>
<th>Treatment Response</th>
<th>BOTOX 50 Units (N=104)</th>
<th>BOTOX 75 Units (N=110)</th>
<th>Placebo (N=108)</th>
<th>BOTOX 50-placebo (95% CI)</th>
<th>BOTOX 75-placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDSS Score change ≥2 (n)</td>
<td>55% (57)</td>
<td>49% (54)</td>
<td>6% (6)</td>
<td>49.3% (38.8, 59.7)</td>
<td>43% (33.2, 53.8)</td>
</tr>
<tr>
<td>&gt;50% decrease in axillary sweat production (%)</td>
<td>81% (84)</td>
<td>86% (94)</td>
<td>41% (44)</td>
<td>40% (26.1, 52.0)</td>
<td>45% (33.3, 56.1)</td>
</tr>
</tbody>
</table>

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

### MEDICATION GUIDE

**BOTOX®**

**BOTOX Cosmetic**

(Boe-tox)

(onabotulinumtoxinA)

for Injection

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

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

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

- Problems breathing or swallowing
- Spread of toxin effects

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

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

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

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

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

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

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

What are BOTOX and BOTOX Cosmetic?

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

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medication (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 medication (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

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

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

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

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

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

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

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

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

Who should not take BOTOX or BOTOX Cosmetic?

Do not take BOTOX or BOTOX Cosmetic if you:

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

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

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

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

Especially tell your doctor if you:
- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), or Xeomin® (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)
- have received an antibiotic by injection
- have received a vaccine
- have recently received an injection of a medication that may cause muscle weakness
- have symptoms such as double vision or drooping eyelids
- have received any other botulinum toxin product in the past. Be sure your doctor knows exactly which product you received.

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

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

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

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

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

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

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

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

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

General information about BOTOX and BOTOX Cosmetic:
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

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

What are the ingredients in BOTOX and BOTOX Cosmetic?
Active ingredient: botulinum toxin type A
Inactive ingredients: human albumin and sodium chloride

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

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc.
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Dysport® is a registered trademark of Ipsen Biopharm Limited Company.
Xeomin® is a registered trademark of Merz Pharma GmbH & Co KGaA.

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72511US14
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