Injection Workbook for Focal Spasticity

Identifying Patients, Advanced Anatomy, and the BOTOX® Treatment Framework

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

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

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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

Please see additional Important Safety Information about BOTOX® inside.
Introduction
This course is designed to help hone your skills in identifying Focal Spasticity patients who may be BOTOX® candidates and implementing the BOTOX® Treatment Framework. We’ll also discuss the resources and services offered by Allergan as part of our commitment to support your practice.

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**Prevalence of common spasticity causes**

1. **Traumatic Brain Injury**: 23%
   - (N = 23,795)
2. **Spinal Cord Injury**: 65%
   - (N = 354)
3. **Multiple Sclerosis**: 84%
   - (N = 20,969)
4. **Adult Cerebral Palsy**: 73%
   - (N = 23,795)
5. **Stroke**: 58%
   - (N = 504)

**Patient considerations**

Presentation is similar across conditions, but it’s important to consider additional factors:

- Traumatic events like a stroke can cause muscle stiffness/tightness, which can interfere with treatment goals
- Conditions like adult cerebral palsy can result in balance difficulties
- Behavioral/cognitive issues can stem from traumatic brain injuries
- Spasticity can present intermittently in chronic conditions, such as multiple sclerosis

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS**

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

Please see additional Important Safety Information about BOTOX® on following pages.
Spasticity can worsen over time

In separate studies of post-stroke patients...

27% of post-stroke patients have signs of spasticity within 6 weeks (N = 86)\textsuperscript{10}

52% of post-stroke patients present with contracture within 6 months in at least 1 joint (N = 165)\textsuperscript{11}

Focal symptoms can manifest in generalized and regional spasticity\textsuperscript{12}

Types of spasticity
- **Generalized**: Increased muscle tightness/tonality that affects widespread portions of the body
- **Regional**: Affects motor skills over a large region of the body, such as the torso or entire left side
- **Focal**: Muscle tightness/tonality that affects 1 or more body parts in an isolated area, which can adversely affect the patient

Notes

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BOTOX\textsuperscript{®} has not been shown to improve upper extremity functional abilities, range of motion at a joint affected by a fixed contracture, or prevent disease progression.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Spread of Toxin Effect
See Boxed Warning.

Please see additional Important Safety Information about BOTOX\textsuperscript{®} on following pages.
Multiple approaches may be useful when assessing Focal Spasticity

Consider using “mild/moderate/severe” framework when capturing observations

<table>
<thead>
<tr>
<th>Ambulatory Patients</th>
<th>Nonambulatory Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluate all affected joints of ankle and toe in all positions: supine, seated, standing, and moving&lt;br&gt;• Observe and evaluate patient’s gait, including gait cycle, as part of determining severity&lt;br&gt;• Measure the time it takes for patient to walk a set distance or get up from seated position and walk to a set point</td>
<td>• Look for potential skin breakdown caused by spasticity&lt;br&gt;• Compare positioning when sitting vs lying down&lt;br&gt;• Determine if patient’s leg position impedes transfers</td>
</tr>
</tbody>
</table>

*Nonambulatory patients were excluded from the BOTOX® lower limb spasticity clinical trial.

Upper limb spasticity

<table>
<thead>
<tr>
<th>Diagnosis Technique</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask the patient what has impacted post-stroke treatment goals</td>
<td>“Muscle tightness” and “stiffness” are usually mentioned the most</td>
</tr>
<tr>
<td>Ask the patient if they have ever taken muscle relaxants</td>
<td>May indicate if another physician had noticed the spasticity</td>
</tr>
<tr>
<td>Have the patient stand up</td>
<td>Helps determine the effect of symptoms on balance and exposes the patient’s limbs</td>
</tr>
<tr>
<td>Shake the patient’s hand</td>
<td>Patient must extend 1 arm, allowing you to check for signs and symptoms in both limbs</td>
</tr>
<tr>
<td>Have patient raise their arms above their head and/or straight out</td>
<td>Allows you to quickly look for effects of spasticity on elbow, wrist, and fingers</td>
</tr>
</tbody>
</table>

It may be time to revisit these patients’ treatment plans

Do you have Focal Spasticity patients in your practice who...

- Are on muscle relaxants and only call in for refills?
- Are meeting treatment goals on current therapy?
- Do not follow their treatment regimen?
- Have finished PT/OT sessions, but want to continue working on symptoms?
- Are contraindicated to certain treatment options?

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.
For each Focal Spasticity patient, establish...

The right goals
Establish specific and realistic goals to guide the course of care

The right plan
Devise a plan to re-evaluate BOTOX® performance throughout treatment sessions

The right muscles/dose
Use goals and postures to identify optimal muscle selection/BOTOX® dose

BOTOX® Treatment Framework Overview

Establish specific and realistic goals to help guide the course of care
- Determine how BOTOX® fits into the overall treatment plan to help achieve these goals
- When using BOTOX®, it’s important to set expectations to help ensure the patient follows the treatment plan

Use patient goals and presenting postures/symptoms to help optimize muscle selection and select the appropriate BOTOX® dose
- Identify muscles contributing to the posture(s) and symptoms
- Isolate which muscles are most problematic and should be targeted, and at which dose

Establish a plan to re-evaluate the performance of BOTOX® over initial and subsequent treatment sessions
- Every patient is different and will respond to treatment differently
- Goals as well as muscles/dose selection should be re-evaluated at each treatment
- Based on patient treatment goals and response to previous treatment, an adjustment in BOTOX® dose or injected muscles may be needed

Notes

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

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

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

Tips to help ensure positive treatment conversations

<table>
<thead>
<tr>
<th>Positive reaction statements</th>
<th>Negative reaction statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized statements and recommendations</td>
<td>Vague or general statements</td>
</tr>
<tr>
<td>Specific and detailed information</td>
<td>Discussion points that seem questioning or defensive</td>
</tr>
<tr>
<td>Clinical data</td>
<td>Words that sound scary or threatening</td>
</tr>
</tbody>
</table>

Get agreement on specific, realistic goals, then evaluate treatment response in relation to those goals

Setting patient expectations can help ensure patients follow the treatment plan

<table>
<thead>
<tr>
<th>Topics</th>
<th>Tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results expectation/schedule</td>
<td>• Reinforce that every patient is different and will respond to BOTOX® differently. Emphasize the importance of coming back every 3 months, once the effect has worn off. • BOTOX® is not a cure, nor is it intended as a substitute for usual standard of care rehabilitation regimens • Regular re-evaluation is important. Patients should return for a 4- to 6-week follow-up evaluation • Adjustments in dose may be needed during future treatment sessions</td>
</tr>
<tr>
<td>Needle pain</td>
<td>• Fine needles are used during injections</td>
</tr>
<tr>
<td>Side effects</td>
<td>• Discuss the common side effects in a patient-friendly way</td>
</tr>
<tr>
<td>Cost</td>
<td>• BOTOX® is covered under many insurance plans and programs are available to help patients with treatment costs</td>
</tr>
</tbody>
</table>

Notes

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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

Individuals with peripheral motor neuropathic diseases, ALS, 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 Warnings and Precautions).

Please see additional Important Safety Information about BOTOX® on following pages.
Steps to use when selecting which muscles to target for injection

1. Based on treatment goals and symptoms, determine which posture(s) to target first

2. Identify muscles contributing to the posture(s) based on physical exam (using EMG/E-Stim if needed)

3. Isolate which muscles are most problematic and should be targeted

4. Select the starting dose for each muscle

Understanding functional anatomy helps guide muscle selection/BOTOX® dose

Approved muscles by posture in Focal Spasticity

<table>
<thead>
<tr>
<th>Posture</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limb spasticity</td>
<td></td>
</tr>
<tr>
<td>Flexed ankle</td>
<td>• Gastrocnemius</td>
</tr>
<tr>
<td></td>
<td>• Soleus</td>
</tr>
<tr>
<td></td>
<td>• Tibialis posterior</td>
</tr>
<tr>
<td>Flexed toes</td>
<td>• Flexor hallucis longus</td>
</tr>
<tr>
<td></td>
<td>• Flexor digitorum longus</td>
</tr>
<tr>
<td>Upper limb spasticity</td>
<td></td>
</tr>
<tr>
<td>Flexed elbow</td>
<td>• Biceps brachii</td>
</tr>
<tr>
<td>Flexion of the wrist</td>
<td>• Flexor carpi radialis</td>
</tr>
<tr>
<td></td>
<td>• Flexor carpi ulnaris</td>
</tr>
<tr>
<td>Clenched fist/finger flexion</td>
<td>• Flexor digitorum profundus</td>
</tr>
<tr>
<td></td>
<td>• Flexor digitorum sublimis</td>
</tr>
<tr>
<td>Thumb in palm</td>
<td>• Adductor pollicis</td>
</tr>
<tr>
<td></td>
<td>• Flexor pollicis longus</td>
</tr>
</tbody>
</table>

Prioritize which muscles/dose to inject based on the established treatment goals

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.
Main muscles involved in lower limb spasticity

Muscles listed in purple boxes are those approved for BOTOX® injection

**Approved Muscles Involved in Common Postures**

<table>
<thead>
<tr>
<th>Ankle Flexors</th>
<th>Toe Flexors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius</td>
<td>Flexor Digitorum Longus</td>
</tr>
<tr>
<td>Soleus</td>
<td>Flexor Hallucis Longus</td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td></td>
</tr>
</tbody>
</table>

| Gastrocnemius (lateral head) | 75 Units divided in 3 sites |
| Flexor Hallucis Longus (hidden) | 50 Units divided in 2 sites |
| Extensor Digitorum Longus* | |
| Extensor Hallucis Longus (hidden)* | |

*For anatomical reference only. Lines indicate muscle location, and do not point out sites for injection.

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Pulmonary Effects in Patients With Compromised Respiratory Status Treated for Spasticity**

Patients with compromised respiratory status treated with BOTOX® for spasticity should be monitored closely.

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

*Muscle action*  
Involved in plantar flexion and flexing the knee

**Proximal attachment**  
Medial head: Popliteal surface of the femur just above the medial condyle  
Lateral head: Lateral surface of the lateral condyle and to the lower part of the corresponding suprcondylar line

**Distal attachment**  
Posterior surface of calcaneus by calcaneal tendon

- Soleus
- Tibialis posterior
- Flexor digitorum longus
- Flexor hallucis longus
- Fibularis longus*

*For anatomical reference only.

**Localization**

Midbelly is located one-quarter the distance from popliteal crease to heel.

**Cross-sectional anatomy: midcalf**

**IMPORTANT SAFETY INFORMATION (continued)**

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

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

**Muscle action**

Involved in plantar flexion

**Proximal attachment**
Posterior surface of the head and proximal quarter of the shaft of the fibula, soleal line and a middle third of the medial border of the tibia, and the fibrous band between the tibia and fibula

**Distal attachment**
Posterior surface of calcaneus by calcaneal tendon

**Other muscles involved in plantar flexion**
- Gastrocnemius
- Tibialis posterior
- Flexor digitorum longus
- Flexor hallucis longus
- Fibularis longus*

*B for anatomical reference only.

**Localization**

Medial or lateral approach is midway to two-thirds the distance from heel to popliteal crease. Can also be approached through the gastrocnemius.

**BOTOX® dose:** 75 Units divided in 3 sites

**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.
Tibialis posterior

Muscle action

Involved in plantar flexion and can also invert and adduct the foot

Proximal attachment
Posterior surface of the interosseous membrane, lateral area on the posterior surface of the tibia between the soleal line above, and medial strip of the posterior fibular surface

Distal attachment
Tuberosity of navicular, medial, and intermediate cuneiforms, and bases of second, third, and fourth metatarsals

Other muscles involved in plantar flexion and/or foot inversion
- Gastrocnemius (plantar flexion only)
- Soleus (plantar flexion only)
- Flexor digitorum longus
- Flexor hallucis longus
- Fibularis longus (plantar flexion only)*
- Tibialis anterior (foot inversion only)*

*For anatomical reference only.

Localization

Lies posterior to interosseous membrane. Medial approach is midway between heel and popliteal crease, which will avoid nerves and vessels near this membrane.

IMPORTANT SAFETY INFORMATION (continued)

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

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

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

**Muscle action**

Involved in flexion of hallux, plantar flexion, and foot inversion

**Proximal attachment**

Distal two-thirds of the posterior surface of the fibula, adjacent interosseous membrane and the posterior crural intermuscular septum, and fascia covering tibialis posterior.

**Distal attachment**

Bases of distal phalanx of hallux

**Other muscles involved in plantar flexion and/or foot inversion**

- Gastrocnemius (plantar flexion only)
- Soleus (plantar flexion only)
- Tibialis posterior
- Flexor digitorum longus
- Tibialis anterior (foot inversion only)*
- Tibialis longus (plantar flexion only)*
- Fibularis longus (plantar flexion only)*

*For anatomical reference only.

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**Localization**

Approach is lateral to Achilles tendon at one-third the distance from heel to popliteal crease and over the fibula.

For anatomical reference only.

**Cross-sectional anatomy: Distal calf**

Approach is lateral to Achilles tendon at one-third the distance from heel to popliteal crease and over the fibula.

**IMPORTANT SAFETY INFORMATION (continued)**

**ADVERSE REACTIONS (continued)**

**Lower Limb Spasticity**

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

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

**Muscle action**¹⁵,¹⁸
Involved in flexion of lateral 4 digits, plantar flexion, and foot inversion

**Localization**²⁶
Midbelly is located one-third to one-half the distance from heel to popliteal crease immediately posterior to tibia.

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**Proximal attachment**
Posterior surface of the tibia medial to tibialis posterior from just below the soleal line and fascia covering tibialis posterior

**Distal attachment**
Bases of distal phalanges of lateral 4 digits

**Other muscles involved in plantar flexion and/or foot inversion**
- Gastrocnemius (plantar flexion only)
- Soleus (plantar flexion only)
- Tibialis posterior
- Flexor hallucis longus
- Fibularis longus (plantar flexion only)*
- Tibialis anterior (foot inversion only)*

*For anatomical reference only.

**BOTOX® dose:** 50 Units divided in 2 sites¹⁴

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**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.
Main muscles involved in upper limb spasticity

Muscles listed in purple boxes are those approved for BOTOX® injection.14,15

Approved Muscles Involved in Common Postures

<table>
<thead>
<tr>
<th>Elbow Flexors</th>
<th>Wrist Flexors</th>
<th>Finger Flexors</th>
<th>Thumb Flexors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps Brachii</td>
<td>Flexor Carpi Radialis</td>
<td>Flexor Digits Profundus</td>
<td>Adductor Pollicis</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis</td>
<td>Flexor Pollicis Longus</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis (Sublimis)</td>
<td></td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis (Sublimis)</td>
<td></td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis (Sublimis)</td>
<td></td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis (Sublimis)</td>
<td></td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis (Sublimis)</td>
<td></td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>Flexor Digits Profundus</td>
<td>Flexor Digits Superficialis (Sublimis)</td>
<td></td>
</tr>
</tbody>
</table>

*For anatomical reference only.
Lines indicate muscle location, and do not point out sites for injection.

IMPORTANT SAFETY INFORMATION (continued)

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

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

*Muscle action*

Supinates the forearm and flexes the elbow

**Localization**

The biceps brachii is located in the anterior surface of the midarm.

**Other muscles involved in elbow flexion/forearm supination**

- Brachialis (flexion only)*
- Supinator (supination only)*
- Brachioradialis (flexion only)*
  
  *For anatomical reference only.

**Proximal attachment**

Short head arises from the coracoid process. Long head arises from the supraglenoid tubercle of the scapula

**Distal attachment**

Radial tuberosity

**BOTOX® dose:** 100 Units to 200 Units divided in 4 sites*14

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**IMPORTANT SAFETY INFORMATION (continued)**

**CONTRAINDICATIONS**

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

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

*Muscle action*

Flexes the wrist and also abducts (radially deviates) the hand

**Other muscles involved in wrist flexion/abduction**

- Flexor carpi ulnaris (flexion only)
- Flexor digitorum superficialis (flexion only)
- Flexor digitorum profundus (flexion only)
- Flexor pollicis longus (flexion only)
- Palmaris longus (flexion only)*
- Extensor carpi radialis longus (abduction only)*
- Abductor pollicis longus (abduction only)*
- Extensor pollicis longus (abduction only)**
  *For anatomical reference only.

**Localization**

The flexor carpi radialis can be located 3 to 4 fingerbreadths down from a line connecting the medial epicondyle and biceps tendon.

*BOTOX® dose: 12.5 Units to 50 Units (1 site)*

**Notes**

*For anatomical reference only.

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS**

Lack of Interchangeability Between Botulinum Toxin Products

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

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

**Muscle action**

Flexes the wrist and also adducts (ulnarily deviates) the hand.

**Proximal attachment**

Humeral head arises from the medial epicondyle via the common flexor tendon. Ulnar head arises from the olecranon and proximal two-thirds of the ulna.

**Distal attachment**

To the pisiform and further to the hamate and fifth metacarpal by pisohamate and pisometacarpal ligaments.

**Other muscles involved in wrist flexion/adduction**

- Flexor carpi radialis (flexion only)
- Flexor digitorum profundus (flexion only)
- Flexor digitorum superficialis (flexion only)
- Flexor pollicis longus (flexion only)
- Palmaris longus (flexion only)*
- Extensor carpi ulnaris (adduction only)*

*For anatomical reference only.

**Localization**

The flexor carpi ulnaris can be located 2 fingerbreadths volar to ulna at the junction of the upper and middle thirds of the forearm.

**BOTOX® dose:** 12.5 Units to 50 Units (1 site)
Flexor digitorum profundus

**Muscle action**

Primarily finger flexion (only muscle capable of flexing the distal interphalangeal joints), but can also flex any or all of the joints over which it passes.

**Proximal attachment**
Upper three-quarters of the anterior and medial surfaces of the ulna.

**Distal attachment**
Palmar surfaces of the bases of the distal phalanges.

**BOTOX® dose**: 30 Units to 50 Units (1 site)

**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.
Flexor digitorum superficialis (sublimis)

**Muscle action**
Primarily finger flexion of proximal interphalangeal (PIP) joints, but can also flex any or all of the joints over which it passes.

**Proximal attachment**
Humeroulnar head arises from the medial epicondyle of the humerus and coronoid process of the ulna. Radial head arises from the upper half of the anterior border of the radius.

**Distal attachment**
Medial and lateral sides of the palmar surface of the middle phalanges.

**Other muscle involved in finger flexion (proximal interphalangeal joints)**
- Flexor digitorum profundus

**Localization**
The flexor digitorum superficialis can be located by grasping the volar surface of the patient’s wrist. Point your index finger to the biceps tendon and locate ulnarly to the tip of the index finger.

**BOTOX® dose:** 30 Units to 50 Units (1 site)

**Notes**

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

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

Please see additional Important Safety information about BOTOX® on following pages.
**Adductor pollicis**

*Muscle action*\(^1\)
Adducts the thumb

**Localization**\(^2\)

The adductor pollicis is located in the proximal end of the first metacarpal bone.

**BOTOX\(^\circ\) dose: 20 Units (1 site)**\(^3\)

**Notes**

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

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

Individuals with peripheral motor neuropathic diseases, ALS, 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\(^\circ\) (see Warnings and Precautions).

Please see additional Important Safety Information about BOTOX\(^\circ\) on following pages.
IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Dysphagia and Breathing Difficulties

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

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

The flexor pollicis longus can be located in the middle of the forearm from the radial aspect just volar to the radius.

Flexor pollicis longus

**Muscle action**

Flexes thumb, but can also be involved in wrist flexion

**Localization**

Proximal attachment
Anterior surface of the radius and the interosseous membrane

Distal attachment
Palmar surface of the base of the distal phalanx of the thumb

**BOTOX® dose:** 20 Units (1 site)
Key principles to setting up an effective treatment plan

- Each patient will respond to treatment differently
- Re-evaluate goals and muscle/dose selection at each treatment
- Adjustments to dose and muscle selection may be needed
- Dosing in initial and subsequent 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®

Help patients understand that their plan may include multiple BOTOX® treatments
Utilize the BOTOX® Treatment Framework when evaluating your next focal spasticity patient

Patient name:

Posture(s):  
- Flexed elbow  
- Flexion of the wrist  
- Thumb in palm  
- Flexed ankle  
- Flexed toes

Symptoms:

Goals:

- Repeat goals back to patient

Expectations:

- BOTOX® is not a cure nor a substitute for usual standard of care
- Dose/muscles may need to be adjusted for future injections
- Fine needles are used during injections
- Patient should return for a 4- to 6-week follow-up evaluation
- Review insurance plans to determine out-of-pocket costs and use of potential savings programs

**Injection 1: Muscles injected/BOTOX® dose**

<table>
<thead>
<tr>
<th>Injected</th>
<th>Approved Muscle¹²</th>
<th>BOTOX® Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius-medial head</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Gastrocnemius-lateral head</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Tibialis posterior</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Flexor hallucis longus</td>
<td>(50 Units divided in 2 sites)</td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum longus</td>
<td>(50 Units divided in 2 sites)</td>
<td></td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>(100 Units to 200 Units divided in 4 sites)</td>
<td></td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>(12.5 Units to 50 Units in 1 site)</td>
<td></td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>(12.5 Units to 50 Units in 1 site)</td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>(30 Units to 50 Units in 1 site)</td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum superficialis</td>
<td>(30 Units to 50 Units in 1 site)</td>
<td></td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>(20 Units in 1 site)</td>
<td></td>
</tr>
<tr>
<td>Flexor pollicis longus</td>
<td>(20 Units in 1 site)</td>
<td></td>
</tr>
</tbody>
</table>

In treating adult patients for 1 or more indications, the maximum cumulative dose should not exceed 400 Units in a 3-month interval.

Please see additional Important Safety Information about BOTOX® on following pages.
4- to 6-week follow-up

Percentage of goals achieved:

Improvements:

Patient comments:

Potential adjustments in muscles/BOTOX® dose:

- Patient scheduled for next treatment session

Injection 2: Muscles injected/BOTOX® dose

<table>
<thead>
<tr>
<th>Injected</th>
<th>Approved Muscle</th>
<th>BOTOX® Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius-medial head</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Gastrocnemius-lateral head</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Tibialis posterior</td>
<td>(75 Units divided in 3 sites)</td>
<td></td>
</tr>
<tr>
<td>Flexor hallucis longus</td>
<td>(50 Units divided in 2 sites)</td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum longus</td>
<td>(50 Units divided in 2 sites)</td>
<td></td>
</tr>
<tr>
<td>Biceps brachii (100 Units to 200 Units)</td>
<td>Divided in 4 sites</td>
<td></td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>(12.5 Units to 50 Units)</td>
<td></td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>(12.5 Units to 50 Units)</td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>(30 Units to 50 Units)</td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum superficialis</td>
<td>(30 Units to 50 Units)</td>
<td></td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>(20 Units)</td>
<td></td>
</tr>
<tr>
<td>Flexor pollicis longus</td>
<td>(20 Units)</td>
<td></td>
</tr>
</tbody>
</table>

In treating adult patients for 1 or more indications, the maximum cumulative dose should not exceed 400 Units in a 3-month interval.

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.
4- to 6-week follow-up

Percentage of goals achieved:

____________________________________________________________________________________

Improvements:

____________________________________________________________________________________

Patient comments:

____________________________________________________________________________________

Potential adjustments in muscles/BOTOX® dose:

____________________________________________________________________________________

☐ Patient scheduled for next treatment session

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

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

Please see additional Important Safety Information about BOTOX® on following pages.
Dilution overview and storage

<table>
<thead>
<tr>
<th>Diluent Added to 200-Unit Vial (0.9% Sodium Chloride Injection)</th>
<th>Diluent Added to 100-Unit Vial (0.9% Sodium Chloride Injection)</th>
<th>Resulting Dose (Units per 0.1 mL)</th>
<th>Resulting Dose (Units per 0.1 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mL</td>
<td>20 Units</td>
<td>1 mL</td>
<td>10 Units</td>
</tr>
<tr>
<td>2 mL</td>
<td>10 Units</td>
<td>2 mL</td>
<td>5 Units</td>
</tr>
<tr>
<td>4 mL</td>
<td>5 Units</td>
<td>4 mL</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>8 mL</td>
<td>2.5 Units</td>
<td>8 mL</td>
<td>1.25 Units</td>
</tr>
<tr>
<td>10 mL</td>
<td>2 Units</td>
<td>10 mL</td>
<td>1 Unit</td>
</tr>
</tbody>
</table>

Note: The product and diluent do not contain a preservative. Administer the 200-Unit vial or 100-Unit vial of BOTOX® within 24 hours after reconstitution in the vial. During this time, BOTOX® solution should be stored in a refrigerator at 2°C to 8°C.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with 0.9% nonpreserved sterile saline (see the table above). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (eg, 25-30 gauge) may be used for superficial muscles, and a longer 22-gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance or nerve stimulation techniques is recommended.

Storage information
- Unopened vials of BOTOX® should be stored in a refrigerator (2°C to 8°C) for up to 36 months
- BOTOX® should be administered within 24 hours after reconstitution of the vial. During this period, BOTOX® should be stored in a refrigerator (2°C to 8°C)

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Upper Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX® for upper limb spasticity include pain in extremity, muscle weakness, fatigue, nausea, and bronchitis.

Please see additional Important Safety Information about BOTOX® on following pages.
Ensure your office is ready for your first BOTOX® injections

• Set up an Allergan account for BOTOX® ordering (1-800-811-4148, Option 2)
• Ensure there is a refrigerator to store BOTOX® vials
• Make sure materials have been ordered:
  – 100- and/or 200-Unit BOTOX® vials
  – 25- to 30-gauge needles for superficial muscles
  – 22-gauge needles for deeper muscles
  – 21-gauge, 2-inch needles for reconstitution
  – 1-mL syringes for injections
  – Appropriately sized syringes for reconstitution
  – Single-use vials of preservative-free, 0.9% sodium chloride (saline)
  – Alcohol swabs for cleaning the rubber stoppers on the saline and BOTOX® vials
  – Adhesive bandages
  – Electromyographic (EMG) or nerve stimulation equipment, if needed
• Review the BOTOX® reconstitution process
• Confirm insurance plan requirements for scheduled patients to ensure appropriate chart-documentation and prior-authorization steps are met (if required)
• Call to remind patients of their scheduled injections

Advantages of using EMG/E-Stim for BOTOX® injections

EMG21
• Can be used to help identify individual muscles contributing to the patient’s condition
• Assists in localizing target-approved muscles and ensuring accurate placement of BOTOX®
• Allows the injector to direct the toxin into more susceptible parts of the fascicle

E-Stim22-24
• Is an option for patients who are sedated, have significant paresis, or are unable to follow voluntary muscle commands
• Facilitates needle placement within a region of a high density of neuromuscular junctions
• May be more accurate than EMG in patients with spasticity because it provides more visual feedback

Notes

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

Please see additional Important Safety Information about BOTOX® on following pages.
Neuroscience Business Practice Specialist (NBPS)

- Works with practices to identify and focus on operational needs (including reimbursement support) that can facilitate the safe and effective use of BOTOX® treatment
- Provides in-person assistance with BOTOX® office processes from the time the patient is first identified through follow-up care

BOTOX® Savings Card

- Helps cover spasticity patients’ out-of-pocket costs for BOTOX® treatment*
- Patients who are eligible receive a prepaid card to be used at participating physician offices, hospitals, and pharmacies for medical expenses

Limitations apply. See page 58 for additional details.

* Covers out-of-pocket costs of BOTOX® and related procedures for up to 4 treatments in a 12-month period.
† Coverage and out-of-pocket costs may vary. Must meet eligibility criteria to qualify.

Have your patients visit BOTOX Savings Card.com or call 1-800-44-BOTOX, Option 4, Option 1

BOTOX ACADEMY®

- Videos and e-lectures on:
  - Injection technique
  - Functional anatomy
  - Muscle localization
  - Reconstitution
- downloadable patient education and office materials

Register at BOTOX Academy.com

Find a BOTOX® Specialist tool

- Help patients seeking treatment find your practice by creating a customized profile

Register at BOTOX Medical.com/Office/Referral

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 page.
IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

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

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


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)

INDICATIONS AND USAGE

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

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

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

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

DOSEAGE AND ADMINISTRATION

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

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)
BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic
migraine (14 headache days or fewer per month) in seven placebo-controlled studies.
Safety and effectiveness have not been established for the prophylaxis of episodic
headaches or migraine.

Important limitations

- Safety and effectiveness have been established for the treatment of chronic
headache, the prophylaxis of episodic migraine, and the treatment of lower limb
spasticity.
- Safety and effectiveness have not been established for other indications
listed above.
- Important limitations for each indication are provided in the full prescribing
information.

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

1.1 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.

Important limitations

- Important limitations for each indication are provided in the full prescribing
information.
- Safety and effectiveness have not been established for the treatment of
overactive bladder with symptoms of urge urinary incontinence, urgency, and
frequency, in adults who have an adequate response to or are tolerant of an
anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition
BOTOX is indicated for the treatment of detrusor overactivity (DO) associated with a
neurologic condition (e.g., SCI, MS) in adults who have an inadequate treatment of
spasticity or are intolerant of antispastic medications.

Important limitations

- Safety and effectiveness have not been established for the treatment of
detrusor overactivity associated with a neurologic condition in adults who have an
adequate response to or are tolerant of antispastic medications.

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 placebo-controlled studies.

1.3 Spasticity

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

Important limitations

- Safety and effectiveness have not been established for the treatment of
upper limb spasticity in adult patients who have an adequate response to or are
tolerant of an antispastic medication.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the
preparation and assay method utilized. They are not interchangeable with other
preparations of botulinum toxin products and, therefore, units of biological activity
of BOTOX cannot be compared to nor converted into units of any other botulinum
toxin products assessed with any other specific assay method [see Warnings and
Precautions (5.2)].
Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3 month interval.

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

2.2 Preparation and Dilution Technique

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

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

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

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

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

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

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

2.3 Bladder Dysfunction

General

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

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

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

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

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

200 Unit Vial of BOTOX

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

100 Unit Vial of BOTOX

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

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

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

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

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

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

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

### 2.4 Chronic Migraine

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

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

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

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

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

### 2.5 Spasticity

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

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

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

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

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

#### Table 4: BOTOX Dosing by Muscle for Lower Limb Spasticity

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

#### Figure 2: Injection Sites for Upper Limb Spasticity

#### Figure 3: Injection Sites for Lower Limb Spasticity

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

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

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

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

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

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

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

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

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

Figure 4: Injection Pattern for Primary Auxiliary Hyperhidrosis

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

2.8 Blepharospasm
For blepharospasm, reconstituted BOTOX is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units/2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpabrae 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. Eccymosis 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).


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

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

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

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

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

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

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

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

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

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

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

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

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

4.3 Urinary Tract Infection or Urinary Retention
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).

[see Warnings and Precautions (5.2, 5.5, 5.6)].
5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

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

5.2 Spread of Toxin Effect

Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include anesthesia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spinal muscular atrophy, in adults with 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.

5.3 Serious Adverse Reactions with Unapproved Use

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

5.4 Hypersensitivity Reactions

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

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

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

5.6 Dysphagia and Breathing Difficulties

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

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

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

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

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

5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely in a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FVC ≤40-80% of predicted value and FEV1/FVC ≤0.75), the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 5).

Table 5: Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 post-injection with up to two treatment cycles with BOTOX or placebo

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

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

In an ongoing double-blind, placebo-controlled, parallel group study in adult patients with dystonia associated with a neurologic condition and restrictive lung disease of neuromuscular etiology (defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS) the event rate in change of Forced Vital Capacity ≥15% or ≥20% was greater in patients treated with BOTOX than in patients treated with placebo (see Table 6).

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

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15%</td>
<td>≥20%</td>
<td>≥15%</td>
</tr>
<tr>
<td>Week 2</td>
<td>0/12 (0%)</td>
<td>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 VI nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.
5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

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

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

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

5.12 Urinary Tract Infections in Patients with Overactive Bladder

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

5.13 Urinary Retention in Patients Treated for Bladder Dysfunction

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

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

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

Overactive Bladder

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

Table 7: Proportion of Patients Catherizing 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 Catherizing for Urinary Retention</td>
<td>6.5% (n=36)</td>
<td>0.4% (n=2)</td>
</tr>
<tr>
<td>Duration of Catheterization for Urinary Retention (Days)</td>
<td>Median</td>
<td>Min, Max</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>1,214</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>3,18</td>
</tr>
</tbody>
</table>

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 8.

5.14 Human Albumin and Transmission of Viral Diseases

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

Table 8: Proportion of Patients Experiencing Urinary Retention following an injection in double-blind, placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BOTOX 100 Units (N=81)</th>
<th>Placebo (N=69)</th>
<th>BOTOX 100 Units (N=526)</th>
<th>Placebo (N=516)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary retention</td>
<td>12.3% (n=10)</td>
<td>0</td>
<td>6.3% (n=33)</td>
<td>0.6% (n=3)</td>
</tr>
</tbody>
</table>

Detrusor Overactivity associated with a Neurologic Condition

In double-blind, placebo-controlled trials in patients with detrusor overactivity associated with a neurologic condition, the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX or placebo is shown in Table 9. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 9: Proportion of Patients not using CIC at baseline and then Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BOTOX 200 Units (N=108)</th>
<th>Placebo (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of Patients Catherizing for Urinary Retention</td>
<td>At any time during complete treatment cycle</td>
<td>30.6% (n=33)</td>
</tr>
<tr>
<td>Duration of Catheterization for Urinary Retention (Days)</td>
<td>Median</td>
<td>289</td>
</tr>
<tr>
<td></td>
<td>Min, Max</td>
<td>1, 530</td>
</tr>
</tbody>
</table>

Among patients not using CIC at baseline, those with MS were more likely to require CIC post-injection than those with SCI (see Table 10).

Table 10: Proportion of Patients by Etiology (MS and SCI) not using CIC at baseline and then Catheterizing for Urinary Retention following an injection in double-blind, placebo-controlled clinical trials

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>MS</th>
<th>SCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 200 Units (N=86)</td>
<td>31% (n=27)</td>
<td>5% (n=4)</td>
</tr>
<tr>
<td>Placebo (N=88)</td>
<td>27% (n=6)</td>
<td>19% (n=3)</td>
</tr>
</tbody>
</table>

At any time during complete treatment cycle
Patients with Diabetes  | Patients without Diabetes
---|---
**BOTOX** 100 Units (N=81) | Placebo (N=69) | **BOTOX** 100 Units (N=526) | Placebo (N=516)

### Urinary Tract Infection

<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>

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.

### 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

- **Urinary tract infection**
- **Urinary retention**
- **Hematuria**

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

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

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

### Chronic Migraine

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

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

---

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

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 12.
Table 14: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

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

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

Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 15.

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

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

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

Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 16. Two hundred thirty-one patients enrolled in a double-blind placebo controlled study (Study 6) received 300 Units to 400 Units of BOTOX, and were compared with 232 patients who received placebo. Patients were followed for an average of 91 days after injection.

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

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

Cervical Dystonia

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

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypotonia, soreness at injection site, asthma, 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 ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

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

In two cases of VII nerve disorder, reduced blinking from BOTOX injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.
Strabismus  
Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2038 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% at all extraocular injection sites. There have been reports of ptosis at all extraocular injection sites, 2% for palpebral injection sites, and 8% for palpebral injection sites. New onset or recurrent strabismus has 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. In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Immunogenicity  
As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to BOTOX therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to BOTOX therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), no patients among 406 migraine patients, no patients among 615 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 data reflect the patients whose test results were considered positive or negative for neutralizing activity to BOTOX in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of neutralizing activity to BOTOX with the incidence of antibodies to other products may be misleading.

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

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

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin [see Warnings and Precautions (5.4, 5.6)]. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8.5 Geriatric Use  
Because elderly patients may be more sensitive to the effects of botulinum toxin, dose reduction may be required. A study of 24 healthy elderly patients showed a trend towards increased sensitivity to BOTOX.

8.6 Pregnancy and Lactation  
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.

8.7 Monitoring Laboratory Tests  
Monitoring laboratory tests has not been established.
8.5 Geriatric Use

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

Overactive Bladder

Of 1324 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 17). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

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

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Urinary Tract Infection</th>
<th>Urinary Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 Years</td>
<td>73 (21%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>65 to 74 Years</td>
<td>53 (30%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>≥75 Years</td>
<td>20 (13%)</td>
<td>8 (9%)</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 symptomatic muscular weakness which could be local, or distant from the site of injection [see Boxed Warning and Warnings and Precautions (5.2, 5.6)]. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

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

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

11 DESCRIPTION

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acetylcholine 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 intradermal injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 0 Units/kg in females) are approximately equal to the maximum recommended human dose of 400 Units on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

In a study to evaluate inadvertent periabdominal 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 urgency 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 inadequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 units of BOTOX or placebo) spaced approximately 1 cm apart into the detrusor muscle.

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 18 and 19, and Figures 5 and 6.
### Table 18: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

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

| **Volume Voided per Micturition**<sup>b</sup> (mL) |                         |                 |                      |         |
| Mean Baseline            | 156                     | 161             |                      |         |
| Mean Change<sup>b</sup> at Week 12** | 38                      | 8               | 30                   | <0.001  |

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

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

<sup>**</sup> Primary timepoint

<sup>a</sup> Primary variable

<sup>b</sup> Secondary variable

### Table 19: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

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

| **Daily Frequency of Micturition Episodes**<sup>b</sup> |                         |                 |                      |         |
| Mean Baseline            | 12.0                    | 11.8            |                      |         |
| Mean Change<sup>b</sup> at Week 12** | -2.3                   | -0.6            | -1.7                 | <0.001  |

| **Volume Voided per Micturition**<sup>b</sup> (mL) |                         |                 |                      |         |
| Mean Baseline            | 144                     | 153             |                      |         |
| Mean Change<sup>b</sup> at Week 12** | 40                      | 10              | 31                   | <0.001  |

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

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

<sup>**</sup> Primary timepoint

<sup>a</sup> Primary variable

<sup>b</sup> Secondary variable

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

14.2 Detrusor Overactivity associated with a Neurologic Condition

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 20 and 21, and Figures 7 and 6. No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.
Table 20: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) Study NDO-1

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
<th>Treatment Difference*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly Frequency of Urinary 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>8.2</td>
<td>(-13.1, -5.3)</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>Maximum Cystometric 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</td>
<td>(89.1, 158.7)</td>
</tr>
<tr>
<td>Maximum Detrusor Pressure during First Involuntary 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
* Primary endpoint
b Secondary endpoint

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

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units</th>
<th>Placebo</th>
<th>Treatment Difference*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly Frequency of Urinary 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</td>
<td>(-14.5, -3.0)</td>
</tr>
<tr>
<td>Mean Change* at Week 12</td>
<td>-19.6</td>
<td>-10.7</td>
<td>-8.9</td>
<td>—</td>
</tr>
<tr>
<td>Maximum Cystometric 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</td>
<td>(101.8, 194.2)</td>
</tr>
<tr>
<td>Maximum Detrusor Pressure during First Involuntary 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
* 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 22).

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

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

* Significantly different from placebo (p<0.05)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.
The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 (no increase in muscle tone) to 4 (limb rigid in flexion or extension). It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

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

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Treatment</th>
<th>Median Change from Baseline in Wrist Flexor Muscle</th>
<th>Median Change from Baseline in Finger Flexor Muscle</th>
<th>Median Change from Baseline in Thumb Flexor Muscle</th>
<th>Median Physician Global Assessment of Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>BOTOX</td>
<td>-2.0*</td>
<td>-1.0*</td>
<td>-1.0*</td>
<td>2.0*</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>Placebo</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Notes:**

1. Primary endpoint at Week 6
2. Secondary endpoints at Week 6
3. Significantly different from placebo (p<0.05)
4. BOTOX injected into both the flexor carpi radialis and ulnaris muscles
5. BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
6. BOTOX injected into the adductor pollicis and flexor pollicis longus muscles
7. Study 2 compared 3 doses of BOTOX with placebo and included 91 patients (BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)) with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 25).

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX low dose (90 Units)</td>
<td>BOTOX mid dose (180 Units)</td>
</tr>
<tr>
<td>Wrist</td>
<td>BOTOX</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>10 Units</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>15 Units</td>
</tr>
<tr>
<td>Finger</td>
<td>7.5 Units</td>
</tr>
<tr>
<td>Flexor Digitorum Profundus</td>
<td>7.5 Units</td>
</tr>
<tr>
<td>Flexor Digitorum Sublimis</td>
<td>7.5 Units</td>
</tr>
<tr>
<td>Elbow</td>
<td>Biceps Brachi</td>
</tr>
</tbody>
</table>

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

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

* Significantly different from placebo (p≤0.05)

††

†

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

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

* Significantly different from placebo (p≤0.010)

†††

†

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX (N=66)</td>
</tr>
<tr>
<td></td>
<td>median change from baseline to week 6 on the modified Ashworth Scale</td>
</tr>
<tr>
<td></td>
<td>Median Physician Global Assessment of Response to Treatment</td>
</tr>
</tbody>
</table>

* Secondary endpoints at Week 6

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>Study 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX (N=14)</td>
</tr>
<tr>
<td></td>
<td>median change from baseline to week 6 on the modified Ashworth Scale</td>
</tr>
<tr>
<td></td>
<td>Median change from baseline to week 6 on the modified Ashworth Scale</td>
</tr>
</tbody>
</table>

* Secondary endpoints at Week 6

††† Other endpoint at Week 6

Table 26: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

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

* Primary endpoint at Week 6

††† 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 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 25).

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

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

<table>
<thead>
<tr>
<th>BOTOX</th>
<th>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale</th>
<th>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale</th>
<th>Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale</th>
<th>Median Physician Global Assessment of Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>low dose</td>
<td>(90 Units) (N=23)</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.5*</td>
</tr>
<tr>
<td>mid dose</td>
<td>(180 Units) (N=21)</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.0*</td>
</tr>
<tr>
<td>high dose</td>
<td>(360 Units) (N=22)</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-1.0*</td>
</tr>
<tr>
<td>Placebo</td>
<td>(N=19)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Primary endpoint at Week 4

††† Secondary endpoints at Week 4

* 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 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units in thumb muscles) or placebo (see Table 28). Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus under EMG guidance (total BOTOX low dose = 30 Units, total BOTOX high dose = 40 Units), or placebo (see Table 28). The duration of follow-up in Study 4 and Study 5 was 12 weeks.
The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4 = very marked worsening to +4 = very marked improvement.

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

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

<table>
<thead>
<tr>
<th>Mean Change from Baseline in Ankle Planter Flexors on the modified Ashworth Scale</th>
<th>BOTOX (N=233)</th>
<th>Placebo (N=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 and 6 Average</td>
<td>-0.8*</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Clinical Global Impression Score by Investigator</th>
<th>BOTOX (N=233)</th>
<th>Placebo (N=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4 and 6 Average</td>
<td>0.9*</td>
<td>0.7</td>
</tr>
</tbody>
</table>

* Significantly different from placebo (p<0.05)

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

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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BOTOX (N=88)</th>
<th>Placebo (N=82)</th>
<th>95% CI on Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CDSS</td>
<td>9.3</td>
<td>9.2</td>
<td>(-2.3, 0.3)</td>
</tr>
<tr>
<td>Change in CDSS at Week 6</td>
<td>-0.3</td>
<td>-1.3</td>
<td>(-4.6, 3.0)</td>
</tr>
<tr>
<td>% Patients with Any Improvement on Physician Global Assessment</td>
<td>31%</td>
<td>51%</td>
<td>(5%, 34%)</td>
</tr>
<tr>
<td>Pain Intensity Baseline</td>
<td>1.8</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Change in Pain Intensity at Week 6</td>
<td>-0.1</td>
<td>-0.4</td>
<td>(-0.7, -0.2)</td>
</tr>
<tr>
<td>Pain Frequency Baseline</td>
<td>1.9</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Change in Pain Frequency at Week 6</td>
<td>-0.0</td>
<td>-0.3</td>
<td>(-0.5, -0.0)</td>
</tr>
</tbody>
</table>

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

**14.5 Cervical Dystonia**

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

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allot 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician’s evaluation of the patients’ status compared to baseline, ranging from -4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 33.
Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

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

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

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

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

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

14.6 Primary Axillary Hyperhidrosis

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

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

In the three study groups the percentage of patients with baseline HDSS score of 3 or 4 who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

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

Table 35: Study 1 - Study Outcomes

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

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

14.7 Blepharospasm

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

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

14.8 Strabismus

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

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes: 100 Units NDC 0023-1145-01 200 Units NDC 0023-3921-02 Vials of BOTOX have a holographic film on the vial label that contains the name “Allergan” within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) If you do not see the lines of rainbow color or the name “Allergan”, do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

Storage Unopened vials of BOTOX should be stored in a refrigerator (2° to 8°C) for up to 36 months. Do not use after the expiration date on the vial. Administer BOTOX within 24 hours of reconstitution; during this period reconstituted BOTOX should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX should be clear, colorless, and free of particulate matter.
1. Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after you receive an injection of BOTOX or BOTOX Cosmetic. These problems could make it unsafe for you to drive a car or do other dangerous activities. See “What should I avoid while receiving BOTOX or BOTOX Cosmetic?”

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

What are BOTOX and BOTOX Cosmetic?

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

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat increased muscle stiffness in ankle and toe muscles in adults with lower limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasms 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 had an allergic reaction to any other botulinum toxin product such as **Myobloc**, **Dysport**, or **Xeomin**.
- have a skin infection at the planned injection site.
- are being treated for urinary incontinence and have a urinary tract infection (UTI).
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing).

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

Tell your doctor about all your medical conditions, including

- 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).
- any other change in the way your face normally looks.
- 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.
- problems emptying your bladder on your own and are being treated for urinary incontinence.
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and 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 recently received an antibiotic by injection.
- take muscle relaxants.
- take an allergy or cold medicine.
- take a sleep medicine.
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners).

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

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

**How should I take BOTOX or BOTOX Cosmetic?**

Your doctor will tell you how often you will receive your dose.

**Your doctor may change your dose of** **BOTOX** **or** **BOTOX Cosmetic**.

Do not start any new medicines until you receive your dose.

**Your doctor will tell you how often you will receive your dose of** **BOTOX** **or** **BOTOX Cosmetic**.

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

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

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

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

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

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

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

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

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

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

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