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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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.
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</td>
<td>• Look for potential skin breakdown caused by spasticity</td>
</tr>
<tr>
<td>• Observe and evaluate patient’s gait, including gait cycle, as part of determining severity</td>
<td>• Compare positioning when sitting vs lying down</td>
</tr>
<tr>
<td>• 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>• 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

Lack of Interchangeability Between Botulinum Toxin Products

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

Spread of Toxin Effect

See Boxed Warning.

Please see additional Important Safety Information about BOTOX® on following pages.
For each Focal Spasticity patient, establish...

**BOTOX® Treatment Framework**

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

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

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

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**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

**The right goals**

**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

**The right muscles/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

**The right plan**

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Serious Adverse Reactions With Unapproved Use**

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

Please see additional Important Safety Information about BOTOX® on following pages.
### 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.</td>
</tr>
<tr>
<td></td>
<td>• Emphasize the importance of coming back every 3 months, once the effect has worn off.</td>
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<tr>
<td></td>
<td>• BOTOX® is not a cure, nor is it intended as a substitute for usual standard of care</td>
</tr>
<tr>
<td></td>
<td>rehabilitation regimens</td>
</tr>
<tr>
<td></td>
<td>• Regular re-evaluation is important. Patients should return for a 4- to 6-week follow-</td>
</tr>
<tr>
<td></td>
<td>up evaluation</td>
</tr>
<tr>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td></td>
<td>patients with treatment costs</td>
</tr>
</tbody>
</table>

### Notes

Please see additional Important Safety Information about BOTOX® on following pages.
The right muscles/dose

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

Muscles involved in action

Symptom severity in those muscles

Most problematic muscles

Approved muscles by posture in Focal Spasticity

<table>
<thead>
<tr>
<th>Posture</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower limb spasticity²</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 spasticity²</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)

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 known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX® (see Warnings and Precautions).

Please see additional Important Safety Information about BOTOX® on following pages.
Injection insights and considerations

General considerations

- The recommended dilution rate for upper and lower limb spasticity is 2:1, meaning put 4 mL of saline into a 200-unit vial or 2 mL into a 100-unit vial.

- Evaluate the anatomy, including relevant function and the effects of treatment on these muscles (e.g., reducing tone), when considering muscle and dose selection.

- Recognize the impact of spasticity on the anatomy, as no 2 patients are alike; muscles may be hypertrophied or atrophied, so thorough assessment of the spastic muscles is critical at each injection cycle.

- Utilize EMG and/or E-Stim guidance to ensure proper needle placement:
  - Accurate needle guidance is necessary to ensure proper muscle selection.
  - When using E-Stim on hyperflexed muscles, passively extend the muscle to allow for flexion.

- Talk patients through the injection session step by step, explaining what they may experience (see, hear, and/or feel):
  - For example: “you are going to feel pressure”, “now a stick and a little burning”, “OK now we are going to move on to the next injection site”, etc.

This information provides suggestions and considerations for injection training but does not constitute professional medical advice.

Before injection

- Examine the patient to identify the muscles contributing to the posture(s) and spasticity.
  - Isolate the involved muscles using a clinical exam as well as EMG and/or E-Stim guidance.

- Verify the needle is securely fastened to the injection syringe.

- Consider the type of needle/syringe to minimize the chance of the needle popping out during the injection.

- Consider using luer lock syringes to prevent the leakage of BOTOX® during the injection.

- Consider lining up the bevel of the needle with the gradations on the syringe so the bevel is facing upward; this will help you read the syringe when injecting.

- Consider discussing the option of using cold spray to numb the injection site(s) with your patients.

- Explain that some injection sites may be more sensitive than others so the pain level can vary with each injection.

During injection

- An assistant may be helpful to position the patient’s spastic limb and maintain stability during the injection.

- Hold the skin at the injection site taut, if possible. Loose skin is more difficult to puncture.

- It may be helpful to hold the hub of the needle with 1 hand like a pencil to ensure better control of the syringe.

- Aspirate to ensure no blood return.

- Consider performing all injections perpendicular to the skin, if possible, to most readily access the muscles involved:
  - To optimally target the muscle, consider angulation of the injection needle and patient’s limb position.

- Insert the needle into the targeted muscle with consistent pressure to reduce pain at the injection site.

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

**Ankle Flexors**
- Gastrocnemius
- Soleus
- Tibialis Posterior

**Toe Flexors**
- Flexor Digitorum Longus
- Flexor Hallucis Longus

#### Anterior view

**Gastrocnemius (lateral head)**
- 75 Units divided in 3 sites

**Gastrocnemius (medial head)**
- 75 Units divided in 3 sites

**Soleus (hidden)**
- 75 Units divided in 3 sites

**Tibialis Anterior**
- For anatomical reference only.

**Fibularis Longus**
- For anatomical reference only.

**Posterior view**

**Gastrocnemius (medial head)**
- 75 Units divided in 3 sites

**Flexor Hallucis Longus (hidden)**
- 75 Units divided in 3 sites

**Flexor Digitorum Longus**
- 50 Units divided in 2 sites

**Soleus (hidden)**
- 75 Units divided in 3 sites

**Tibialis Posterior (hidden)**
- 75 Units divided in 3 sites

**Fibularis Longus**
- For anatomical reference only.

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

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**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 supracondylar line

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

**Other muscles involved in plantar flexion**
- Soleus
- Tibialis posterior
- Flexor digitorum longus
- Flexor hallucis longus
- Tibialis longus*
- Fibularis longus*
  *For anatomical reference only.

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

**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.
**Gastrocnemius (continued)**

*Injection considerations*

- Gastrocnemius and soleus muscles make up the triceps surae and should be thought of as a complex
- The gastrocnemius crosses both the knee and ankle
- Position patient prone when possible
- Consider following a straight line from proximal to distal in both the medial and lateral heads when injecting the 3 sites
- Avoid going too distal so that the tendinous area is not inadvertently injected
- Gastrocnemius is thinner than the soleus, so consider needle depth carefully

**Notes**

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**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**Human Albumin and Transmission of Viral Diseases**

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

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

Muscle action

Involved in plantar flexion

- Gastrocnemius
- Tibialis posterior
- Flexor digitorum longus

BOTOX® dose: 75 Units divided in 3 sites

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

- Flexor hallucis longus
- Tibialis longus*

*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.

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.
Soleus (continued)

Injection considerations

- Soleus and gastrocnemius muscles make up the triceps surae and should be thought of as a complex.
- Position patient prone when possible
  - Activate the muscle with the knee flexed and have the patient plantarflex
- The soleus is deep and distal to the gastrocnemius, slightly lateral to the midline down the long axis of the leg
- Consider following a straight line from proximal to distal when injecting the 3 sites
- Consider advancing the needle to avoid further skin punctures
- Avoid going too distal to avoid the tendinous area. Stay above the midcalf

Notes

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**Localization**

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

**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.

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

**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.
Tibialis posterior (continued)

Injection considerations

- Position the patient supine with his/her leg extended, when possible
  - Recommend using established guidance techniques as the muscle may be difficult to locate
- This muscle runs the length of the tibia so divide the leg into thirds
- Consider even distribution from proximal to distal when injecting the 3 sites
- Use a medial approach to avoid the neurovascular bundle

Notes

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.
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)*
  - Flexor digitorum longus (plantar flexion only)*
  - Tibialis posterior (foot inversion only)*

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

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

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

*For anatomical reference only.

**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 hallucis longus (continued)

Injection considerations

- Position the patient supine, when possible
- This muscle starts at the lateral side of the leg and comes across the medial side at the ankle, but closer to the tendon than the bone
- Based on the anatomical structure, consider a lateral approach

- Consider targeting 1/3 to 2/3 proximal, respectively, to the lateral malleolus, 1/3 of the way up from the back of the heel to the knee when injecting the 2 sites
  - Consider placing the needle midway to 3/4 distally down the leg
- Inject this muscle when the great toe has flexion spasticity

Notes

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

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

Spread of Toxin Effect

See Boxed Warning.

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

Muscle action

Involved in flexion of lateral 4 digits, plantar flexion, and foot inversion

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
- Tibialis anterior (foot inversion only)*
- Fibularis longus (plantar flexion only)*

*For anatomical reference only.

BOTOX® dose: 50 Units divided in 2 sites

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Serious Adverse Reactions With Unapproved Use
Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, 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 longus (continued)

Injection considerations

- The patient can be positioned supine, prone, or sitting.
- This muscle starts at the medial part of the leg and continues laterally to the foot.
- Have patients bend their toes while using EMG to help localize the muscle. With E-Stim you want them to relax the muscle, not bend their toes.
- Consider targeting the middle and 3/4 distally down the leg when injecting the 2 sites.

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.
Main muscles involved in upper limb spasticity

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

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 Digitorum profundus</td>
<td>Adductor Pollicis</td>
</tr>
<tr>
<td>Flexor Carpi Ulnaris</td>
<td>Flexor Digitorum superficialis (sublimis)</td>
<td></td>
<td>Flexor Pollicis Longus</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>12.5 Units to 50 Units in 1 site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units in 1 site</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anterior view

Biceps Brachii
100 Units to 200 Units divided in 4 sites

Flexor Carpi Radialis
12.5 Units to 50 Units in 1 site

Flexor Carpi Ulnaris
12.5 Units to 50 Units in 1 site

Flexor Pollicis Longus
20 Units in 1 site

Adductor Pollicis
20 Units in 1 site

Biceps Brachii
100 Units to 200 Units divided in 4 sites

Flexor Carpi Radialis
12.5 Units to 50 Units in 1 site

Flexor Carpi Ulnaris
12.5 Units to 50 Units in 1 site

Flexor Pollicis Longus
20 Units in 1 site

Adductor Pollicis
20 Units in 1 site

Brachialis*
Brachioradialis*
Supinator*
Extensor Carpi Radialis Longus*
Extensor Carpi Ulnaris*
Abductor Pollicis Longus*
Extensor Digi Torque (hidden)
Extensor Pollicis Brevis*
Flexor Carpi Radialis
Flexor Carpi Ulnaris
Flexor Digtitorum Profundus (hidden)
Flexor Digtitorum Superficialis (sublimis)
Flexor Pollicis Longus
Adductor Pollicis

*For anatomical reference only.

Lines indicate muscle location, and do not point out sites for injection.

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 known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX® (see Warnings and Precautions).

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

**Muscle action**

Supinates the forearm and flexes the elbow

![Diagram of Biceps brachii](image)

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

**Distal attachment**
Radial tuberosity

**Other muscles involved in elbow flexion/forearm supination**
- Brachialis (flexion only)*
- Supinator (supination only)*
- Brachioradialis (flexion only)*

*For anatomical reference only.

**Localization**

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

---

**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.
Biceps brachii (continued)

Injection considerations

• Extend the arm, if possible, and approach the muscle through the anterior aspect of the bicep to avoid the vascular areas
• Consider using an inverted V pattern at the junction of the middle and lower third of the muscle when injecting the 4 sites
• Biceps muscles may be thinner in some individuals

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.
Flexor carpi radialis

**Muscle action**  
Flexes the wrist and also abducts (radially deviates) the hand

**Proximal attachment**  
Medial epicondyle via the common flexor tendon

**Distal attachment**  
Palmar surface of the base of the second metacarpal

**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)*
- Extensor pollicis brevis (abduction only)*

*B 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.

**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.
Flexor carpi radialis (continued)
Injection considerations

- If possible, place the arm in a neutral position, put 1 finger on the bicep tendon and 1 finger on the medial epicondyle, bisect the line, and palpate the muscle with passive flexion
- Consider injecting in the proximal 1/3 of the forearm, in the largest part of the muscle
  - If you are in the mid forearm, you may be in the wrong muscle
- Avoid going too deep to avoid inadvertent injection of neighboring muscles

Notes

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

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

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)*

*B 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.

*B for anatomical reference only.

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

**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.

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*For anatomical reference only.
**Flexor carpi ulnaris (continued)**

*Injection considerations*

- If possible, position the limb in a comfortable position and localize using 2 fingerbreadths volar to the ulna.
- Consider targeting the injection site in the ulnar portion of the volar forearm.
- This muscle is very thin and superficial, so be aware of the surrounding nerves, arteries, and veins that are in the trajectory of the needle path.

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**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 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

*Localization*

The flexor digitorum profundus can be located by placing the tip of the little finger on the olecranon and ring, middle, and index fingers along the shaft of ulna. Locate just beyond the tip of the index finger just ulnarly to the shaft—1 cm to 5 cm deep.

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

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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.
Flexor digitorum profundus (continued)

Injection considerations

- If possible, position the elbow bent and forearm vertical
- Consider injecting the mid forearm, proximal toward the elbow, at the largest part of the muscle. Note that the muscle is deeper in the anatomy of the arm
- If there is more spasticity in fingers 2 and 3, advance your needle more laterally
- The finger flexors are located in the middle half of the forearm. Target this muscle when the distal interphalangeal joints are closed
- Be aware of the surrounding nerves, arteries, and veins that are in the trajectory of the needle path

Notes

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®.
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.

Localization

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

BOTOX® dose: 30 Units to 50 Units (1 site)
Flexor digitorum superficialis (sublimis) (continued)

Injection considerations

- Target this muscle when the proximal interphalangeal (PIP) joints are open and spastic.
- The finger flexors are located in the middle third to half of the forearm. Localization of this muscle may be difficult.
- Passively extend the PIP joints to help localize the muscle. The use of E-Stim is highly recommended.
- Once the muscle has been anatomically localized, use EMG and/or E-Stim guidance to further identify the muscle.
- If the fingers can be stretched out, it makes identifying the superficialis and profundus with E-Stim easier.

Notes

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

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

Spread of Toxin Effect

See Boxed Warning.

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

Muscle action
Adducts the thumb

Proximal attachment
Oblique head is attached to the capitae bone, the bases of the second and third metacarpal bones, the palmar ligaments of the carpus, and the sheath of the tendon of flexor carpi radialis. The transverse head is attached to the distal two-thirds of the palmar surface of the third metacarpal bone.

Distal attachment
Base of the proximal phalanx of the thumb

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

BOTOX® dose: 20 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, 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.
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.
Flexor pollicis longus

**Muscle action**
Flexes thumb, but can also be involved in wrist flexion.

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

**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)²

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

Please see additional Important Safety Information about BOTOX® on following pages.
Flexor pollicis longus (continued)

Injection considerations

- Target this muscle when interphalangeal flexor joint in the thumb is spastic
- When localizing this muscle, note that it may be more distal in spastic patients
  - Use passive maneuvers to help localize. EMG and/or E-Stim guidance is highly recommended
  - Stabilize the joints prior to injection
- It may be helpful to palpate the radius and then slide to the ulnar side of the radius. Consider inserting the needle volar and lateral to the midline about 2/3 the distance of the forearm from the medial epicondyle

Notes
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®

Injection 1
- Establish goals and set expectations with the patient
- Determine the right muscles/dose needed for a proper initial response
- Have the patient schedule a 4- to 6-week follow-up, as well as their next injection

4-6 Week Follow-up
- Measure response to treatment, point out improvements and discuss side effects
- Based on response, discuss re-treatment and plan for potential muscle/dose adjustments for next injection if needed
- Re-treatment can occur when the effect of the toxin has worn off, as soon as 12 weeks after previous injection

Subsequent Injections
- Check on goal status and if modification is needed
- Determine if adjustments in muscle/dose are needed based on response seen at follow-up and day of injection
- At the end of the treatment session, have the patient schedule a 4- to 6-week follow-up

What’s next?
- Measure response to treatment, point out improvements and discuss side effects
- Based on response, discuss re-treatment and plan for potential muscle/dose adjustments for next injection if needed
- Re-treatment can occur when the effect of the toxin has worn off, as soon as 12 weeks after previous injection

Help patients understand that their plan may include multiple BOTOX® treatments

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.
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

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.

Injection 1: 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 divided in 4 sites)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor carpi radialis (12.5 Units to 50 Units in 1 site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor carpi ulnaris (12.5 Units to 50 Units in 1 site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum profundus (30 Units to 50 Units in 1 site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor digitorum superficialis (30 Units to 50 Units in 1 site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adductor pollicis (20 Units in 1 site)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexor pollicis longus (20 Units in 1 site)</td>
<td></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.
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 Muscle²</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>
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<td>Tibialis posterior</td>
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<tr>
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</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</td>
<td>(50 Units divided in 4 sites)</td>
<td></td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
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<td></td>
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<td>Adductor pollicis</td>
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<td></td>
</tr>
<tr>
<td>Flexor pollicis longus</td>
<td>(20 Units in 1 site)</td>
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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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

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

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.
Dilution overview and storage

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)

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.
Allergan resources and support

**Business Practice Specialist (BPS)**

- 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 eligible 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 78 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 BOTOXSavingsCard.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 BOTOXAcademy.com

**Find a BOTOX® Specialist tool**

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

Register at BOTOXMedical.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 pages.
IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

Co-administration of BOTOX® or other agents interfering with neuromuscular transmission (e.g., 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.
INDICATIONS AND USAGE

WARNING: DISTANT SPREAD OF TOXIN EFFECT

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

• Warnings and Precautions (5.5, 5.7, 5.13, 5.14) 4/2017

INDICATIONS AND USAGE

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

• Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)

• Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)

• Prophylaxis of headaches in adult patients with chronic migraine (>15 days per month with headache lasting 4 hours a day or longer) (1.2)

• Treatment of spasticity in adult patients (1.3)

• Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)

• Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)

• Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)

• Treatment of strabismus in patients ≥12 years of age (1.6)

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

• Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)

• Treatment of upper or lower limb spasticity in pediatric patients (1.3)

• Treatment of hyperhidrosis in body areas other than axillary (1.5)

DOSE 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 dosage 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)

• Axillary Hyperhidrosis: 50 Units per axilla (2.7)

• Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.8)

• Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX (2.9)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

• Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.4, 6)

• Infection at the proposed injection site (4.2)

• Intradetrusor Injections: Urinary Tract Infection or Urinary Retention (4.3)

WARNINGS AND PRECAUTIONS

• Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.1, 11)

• Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.6)

• Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)

• Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)

• Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)

• Use in patients with compromised retinal circulation may occur with BOTOX treatment of blepharospasm (5.8)

• Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of strabismus (5.9)

• Use with caution in patients who have a neurologic condition (e.g., spinal cord injury, multiple sclerosis) (5.10)

• Use with caution in patients with diabetes mellitus (5.13)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and >placebo) are (6.1):

• OAB: urinary tract infection, dysuria, urinary retention

• Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention

• Chronic Migraine: neck pain, headache

• Spasticity: pain in extremity

• Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis

• Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

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

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

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

• Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the prophylaxis of headaches in chronic migraine, treatment of OAB, detrusor overactivity associated with a neurologic condition, spasticity, and axillary hyperhidrosis; in patients under 16 years of age for treatment of cervical dystonia; and in patients under 12 years of age for treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 4/2017
3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

4.2 Infection at the Injection Site(s)

4.3 Urinary Tract Infection or Urinary Retention

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

5.2 Spread of Toxin Effect

5.3 Serious Adverse Reactions with Unapproved Use

5.4 Hypersensitivity Reactions

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

5.6 Dysphagia and Breathing Difficulties

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

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

5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

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

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

5.12 Urinary Tract Infections in Patients with Overactive Bladder

5.13 Urinary Retention in Patients Treated for Bladder Dysfunction

5.14 Human Albumin and Transmission of Viral Diseases

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.3 Post-Marketing Experience

FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include: asthma, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and have been reported 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 at lower doses. [See Warnings and Precautions (5.2)]

1 INDICATIONS AND USAGE

1.1 Bladder Dysfunction

Overactive Bladder

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

Detrusor Overactivity associated with a Neurologic Condition

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

1.2 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (>15 days per month with headache lasting 4 hours a day or longer).

Important Limitations

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

1.3 Spasticity

Upper Limb Spasticity

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

Lower Limb Spasticity

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

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

7.2 Anticholinergic Drugs

7.3 Other Botulinum Neurotoxin Products

7.4 Muscle Relaxants

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

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11 DESCRIPTION

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12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

14.2 Detrusor Overactivity associated with a Neurologic Condition

14.3 Chronic Migraine

14.4 Spasticity

14.5 Cervical Dystonia

14.6 Primary Axillary Hyperhidrosis

14.7 Blepharospasm

14.8 Strabismus

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

Important Limitations

Safety and effectiveness of BOTOX have not been established for the treatment of other upper or lower limb muscle groups. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years.

BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

1.4 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.5 Primary Axillary Hyperhidrosis

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

Important Limitations

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

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

1.6 Blepharospasm and Strabismus

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

2 DOSEAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin product 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)** |
|-------------------------|-----------------|-------------------------|---------------------|
| Diluent* Added to 100 Unit Vial | Resulting Dose Units per 0.1 mL | Diluent* Added to 200 Unit Vial | Resulting Dose Units per 0.1 mL |
| 1 mL | 10 Units | 1 mL | 20 Units |
| 2 mL | 5 Units | 2 mL | 10 Units |
| 4 mL | 2.5 Units | 4 mL | 5 Units |
| 8 mL | 1.25 Units | 8 mL | 2.5 Units |
| 10 mL | 1 Unit | 10 mL | 2 Units |

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

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

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

2.3 Bladder Dysfunction

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

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

2.3.1.1 200 Unit Vial of BOTOX
- Reconstitute a 200 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 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 containing each 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.

2.3.1.2 100 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 re-injection 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 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

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

<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>Procuer</td>
<td>5 Units in 1 site</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 Units divided in 6 sites</td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 Units divided in 8 sites</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 Units divided in 6 sites</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group</td>
<td>20 Units divided in 4 sites</td>
</tr>
<tr>
<td><strong>Total Dose:</strong></td>
<td><strong>155 Units divided in 31 sites</strong></td>
</tr>
</tbody>
</table>

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

2.5 Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient’s response to previous treatment, or adverse event history with BOTOX. The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with techniques such as needle electromyographic guidance may be useful.

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

Upper Limb Spasticity

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

Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity

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

2.6 Cervical Dystonia

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

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

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

2.7 Primary Auxiliary Hyperhidrosis

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

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

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

**Figure 4.** Injection Pattern for Primary Auxiliary Hyperhidrosis

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

2.8 Blepharospasm

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

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

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

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

2.9 Strabismus

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

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection. The recommended dilution is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

**Initial Doses in Units**

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

**Subsequent Doses for Residual or Recurrent Strabismus**

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

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

4.2 Infection at the Injection Site(s)

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

4.3 Urinary Tract Infection or Urinary Retention

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

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

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

5.2 Spread of Toxin Effect

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

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

5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.
5.4 Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the cause of the reaction could not be reliably determined.

5.5 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX [see Warnings and Precautions (5.2, 5.6)].

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 swallowing or breathing [see Warnings and Precautions (5.2)].

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

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

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

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

5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neuromologic Condition
Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV1 40-80% of predicted value and FVC ≤ 0.75), the event rate in change of Forced Vital Capacity (FVC) >15% or >20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 5).

Table 5: Event Rate Per Patient Treatment Cycle Among Patients with Reduced Lung Function Who Experienced at Least a 15% or 20% Decrease in FVC From Baseline at Week 1, 6, 12 Post-injection with Up to Two Treatment Cycles with BOTOX or Placebo

<table>
<thead>
<tr>
<th>Week</th>
<th>≥15%</th>
<th>≥20%</th>
<th>≥15%</th>
<th>≥20%</th>
<th>≥15%</th>
<th>≥20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>4%</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Week 6</td>
<td>7%</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Week 12</td>
<td>10%</td>
<td>5%</td>
<td>2%</td>
<td>1%</td>
<td>4%</td>
<td>1%</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)].

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>BOTOX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 Units</td>
<td>200 Units</td>
</tr>
<tr>
<td>≥15%</td>
<td>≥20%</td>
</tr>
<tr>
<td>Week 2</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>2/13 (15%)</td>
</tr>
<tr>
<td>Week 12</td>
<td>0/12 (0%)</td>
</tr>
</tbody>
</table>

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

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

5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were 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 prompt 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 (6.4)]. 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 10: Proportion of Patients by Etiology (MS and SCI) Not Using CIC at Baseline

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>BOTOX 100 Units (N=552)</th>
<th>Placebo (N=542)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At any time during complete treatment cycle</td>
<td>6.5% (n=36)</td>
<td>0.4% (n=2)</td>
</tr>
</tbody>
</table>

Duration of Catheterization for Urinary Retention (Days)

<table>
<thead>
<tr>
<th>Median</th>
<th>Min, Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>1,214, 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.

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

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units (N=81)</td>
<td>Placebo (N=69)</td>
</tr>
<tr>
<td>12.3% (n=10)</td>
<td>6.3% (n=33)</td>
</tr>
</tbody>
</table>

Detrusor Overactivity associated with a Neurologic Condition

In two double-blind, placebo-controlled trials in patients with detrusor overactivity associated with a neurologic condition (NDO-1 and NDO-2), the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX 200 Units or placebo is shown in Table 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>At any time during complete treatment cycle</td>
<td>30.6% (n=33)</td>
<td>6.7% (n=7)</td>
</tr>
</tbody>
</table>

Duration of Catheterization for Urinary Retention (Days)

<table>
<thead>
<tr>
<th>Median</th>
<th>Min, Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>289</td>
<td>1,530, 2,379</td>
</tr>
</tbody>
</table>

Among patients not using CIC at baseline, those with Multiple Sclerosis (MS) were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 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>At any time during complete treatment cycle</td>
<td>31% (n=27)</td>
<td>5% (n=4)</td>
</tr>
</tbody>
</table>

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

5.14 Human Albumin and Transmission of Viral Diseases

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

6 ADVERSE REACTIONS

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

- Spread of Toxin Effects [see Warnings and Precautions (5.2)]
- Serious Adverse Reactions with Unapproved Use [see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions [see Contraindications (5.1) and Warnings and Precautions (5.4)]
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders [see Warnings and Precautions (5.5)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition [see Warnings and Precautions (5.7)]
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm [see Warnings and Precautions (5.8)]
- Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus [see Warnings and Precautions (5.9)]
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity [see Warnings and Precautions (5.10)]
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition [see Warnings and Precautions (5.11)]
- Urinary Tract Infections in Patients with Overactive Bladder [see Warnings and Precautions (5.12)]
- Urinary Retention in Patients Treated for Bladder Dysfunction [see Warnings and Precautions (5.13)]

6.1 Clinical Trials Experience

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

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

In general, adverse reactions occur within the first week following injection of BOTOX and, while generally transient, may have a duration of several months or longer. Localized pain, injection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (including syncope, hypotension), which may require appropriate medical therapy. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin [see Warnings and Precautions (5.2)].

Overactive Bladder

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

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

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

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

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 12.
The incidence of URI 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.

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

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

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

The following adverse reactions with BOTOX 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 51 weeks): urinary tract infections (26%), urinary retention (17%), constipation (4%), musculoskeletal weakness (4%), dysuria (4%), gait disturbance (3%), and residual urine volume (3%).

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

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

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

### Table 12: Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Placebo (N=69)</th>
<th>BOTOX 100 Units (N=81)</th>
<th>Placebo (N=516)</th>
<th>BOTOX 100 Units (N=526)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection (UTI)</td>
<td>25 (31%)</td>
<td>8 (12%)</td>
<td>135 (26%)</td>
<td>51 (10%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 200 Units (N=282)</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>

### Table 14: Adverse Reactions Reported by >2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection (NDO-3)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>BOTOX 100 Units (N=66)</th>
<th>Placebo (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>17 (26%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Bacteruria</td>
<td>6 (9%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>10 (15%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>3 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Residual urine volume*</td>
<td>11 (17%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX 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 paresthesia</td>
<td>15 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (3%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (9%)</td>
<td>19 (3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (4%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (4%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (3%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>Muscle spasm</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 included: 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.

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

<table>
<thead>
<tr>
<th>Adverse Reactions by System Organ Class</th>
<th>BOTOX 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.
Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)

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

Cervical Dystonia
In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were 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, hypertension, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dysphagia have also 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 (5.2, 5.6)].

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

Primary Auxillary 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 rhinorrhea, non-axillary sweating, injection, 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 dryness (6%).

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

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

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

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

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

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

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%) and no patients among 406 migraine patients with analyzed specimens developed the presence of neutralizing antibodies. In overactive bladder patients with analyzed specimens from the two phase 3 studies and the open-label extension study, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. Response to subsequent BOTOX treatment was not different following seroconversion in these three patients.

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

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

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

6.3 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; hypothyroidism; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasis; and visual disturbances.

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

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

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

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

8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

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

Prophylaxis of Headaches in Chronic Migraine

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

Spasticity

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

Ayillary Hyperhidrosis

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

Cervical Dystonia

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

Blepharospasm and Strabismus

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

8.5 Geriatric Use

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

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% were 65 years of age or older, and 14.7% were 75 years of age or older. Adverse reactions of 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 18). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

Table 18: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Placebo</th>
<th>BOTOX 100 Units</th>
<th>BOTOX 160 Units</th>
<th>Placebo 151</th>
<th>BOTOX 100 Units 94</th>
<th>Placebo (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 Years</td>
<td>24 (10%)</td>
<td>46 (16%)</td>
<td>57 (20%)</td>
<td>16 (9%)</td>
<td>25 (15%)</td>
<td>10 (11%)</td>
</tr>
<tr>
<td>65 to 74 Years</td>
<td>52 (31%)</td>
<td>72 (20%)</td>
<td>85 (26%)</td>
<td>29 (18%)</td>
<td>38 (21%)</td>
<td>20 (17%)</td>
</tr>
<tr>
<td>≥75 Years</td>
<td>45 (31%)</td>
<td>60 (23%)</td>
<td>70 (29%)</td>
<td>25 (18%)</td>
<td>38 (23%)</td>
<td>25 (26%)</td>
</tr>
</tbody>
</table>

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

10 ODOSOSAGE

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

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

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/nnm5232a8.htm.

11 DESCRIPTION

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hal strain Clostridium botulinum type A, and intended for intramuscular, intradermal and subcutaneous 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 and is performed on a unit basis. The potency of BOTOX relative to a reference standard is determined using a cell-based potency assay.

The potency of BOTOX relative to a reference standard is determined using a cell-based potency assay. The potency of BOTOX relative to a reference standard is determined using a cell-based potency assay.
**Table 19: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1**

<table>
<thead>
<tr>
<th>Variable</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>Mean Baseline</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 2</td>
<td>-2.6</td>
<td>-1.0</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 6</td>
<td>-2.8</td>
<td>-1.0</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12**</td>
<td>-2.5</td>
<td>-0.9</td>
<td>-1.6 (-2.1, -1.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</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>Mean Baseline</td>
<td>5.5</td>
<td>5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 2</td>
<td>-2.7</td>
<td>-1.1</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 6</td>
<td>-3.1</td>
<td>-1.3</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12**</td>
<td>-3.0</td>
<td>-1.1</td>
<td>-1.9 (-2.5, -1.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

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

** Primary timepoint

† Primary variable

Secondary variable

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acetylcholine receptors on motor or autonomic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles associated with fusion. 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 intradurally, BOTOX produces partial chemical denervation of the sweat gland resulting in local reduction in sweating. Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in 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) in untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the human dose of 400 Units on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary timepoint of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 19 and 20, and Figures 5 and 6.
The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19–24 weeks for the BOTOX 100 Unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL, and patients must have reported at least 2 urinary incontinence episodes over 3 days.

14.2 Detrusor Overactivity associated with a Neurologic Condition

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 21 and 22, and Figures 7 and 8.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.
The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295–337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 100 Units</th>
<th>Placebo</th>
<th>Treatment Difference*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily Frequency of Urinary Incontinence Episodes</strong>(b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>66</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>4.2</td>
<td>4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change(^\text{a}) at Week 2</td>
<td>-2.9</td>
<td>-1.2</td>
<td>-1.7</td>
<td></td>
</tr>
<tr>
<td>Mean Change(^\text{a}) at Week 6**</td>
<td>-3.4</td>
<td>-1.1</td>
<td>-2.3 (-3.0, -1.7)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change(^\text{a}) at Week 12</td>
<td>-2.7</td>
<td>-1.0</td>
<td>-1.8</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity</strong> <em>(mL)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>62</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>248.9</td>
<td>245.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change(^\text{a}) at Week 6**</td>
<td>134.4</td>
<td>3.5</td>
<td>130.9 (94.8, 167.0)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction</strong> <em>(cmH\textsubscript{2}O)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>25</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>42.4</td>
<td>39.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change(^\text{a}) at Week 6**</td>
<td>-19.2</td>
<td>2.7</td>
<td>-21.9 (-37.5, -6.9)</td>
<td></td>
</tr>
</tbody>
</table>

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

\(\text{** Primary timepoint} \)

\(\text{a Primary endpoint} \)

\(\text{b Secondary endpoint} \)

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

### 14.3 Chronic Migraine

BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had \(\geq15\) headache days lasting 4 hours or more, with \(\geq50\%\) being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 24).

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

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

\(^*\) Significantly different from placebo (p<0.05)
Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.

Figure 9: Mean Change from Baseline in Number of Headache Days for Study 1

![Graph showing mean change from baseline in number of headache days for Study 1](image1)

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

![Graph showing mean change from baseline in number of headache days for Study 2](image2)

### 14.4 Spasticity

#### Upper Limb Spasticity

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

Study 1 included 126 patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, and if necessary into the adductor pollicis and flexor pollicis longus muscles (Table 25). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

#### Upper Limb Spasticity

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, and flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 26).

#### Muscles Injected

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

* injected only if spasticity is present in this muscle

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

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

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

<table>
<thead>
<tr>
<th>Muscles Injected</th>
<th>BOTOX (N=64)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>-2.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>Flexor Carpi Radialis</td>
<td>-1.0*</td>
<td>0.0</td>
</tr>
<tr>
<td>Finger</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>Elbow</td>
<td>2.0*</td>
<td>0.0</td>
</tr>
</tbody>
</table>

1 Primary endpoint at Week 6
2 Secondary endpoint 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

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments. Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 28.
Study 5 was 12 weeks.

d = 40 Units), or placebo (see Table 30). The duration of follow-up in Study 4 and pollicis longus under EMG guidance (total BOTOX low dose = 30 Units, total BOTOX high dose = 20 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units who were at least 6 months post-stroke. In Study 4, patients received 20 Units of Study 4 included 170 patients (87 BOTOX and 83 placebo) 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 months post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 27).

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 27).

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 29.

Table 29: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

<table>
<thead>
<tr>
<th>BOTOX Dose</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>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose (90 Units)</td>
<td>-1.0*</td>
<td>-1.0*</td>
<td>-0.5</td>
</tr>
<tr>
<td>Mid dose (180 Units)</td>
<td>-1.0</td>
<td>-0.5</td>
<td>-1.0</td>
</tr>
<tr>
<td>High dose (360 Units)</td>
<td>-1.5*</td>
<td>-1.0*</td>
<td>-0.5</td>
</tr>
<tr>
<td>Placebo (N=19)</td>
<td>-0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Table 30: 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>
<th>Number of Injection Sites for Studies 4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX (Units)</td>
<td>Volume (mL)</td>
<td>BOTOX low dose (Units)</td>
</tr>
<tr>
<td>Thumb Adductor Pollicis</td>
<td>20</td>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20</td>
<td>0.4</td>
<td>15</td>
</tr>
</tbody>
</table>

†† † Significantly different from placebo (p≤0.001)
††† BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function]) are presented in Table 31.

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

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

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

The primary endpoint at Week 6

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

Table 32: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

<table>
<thead>
<tr>
<th>BOTOX (30 Units) (N=14)</th>
<th>Placebo (40 Units) (N=43)</th>
<th>Placebo (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scalehm</td>
<td>-1.0</td>
<td>-0.5*</td>
</tr>
<tr>
<td>Median Change in Clinical Global Impression Score by Physician††</td>
<td>1.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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

Lower Limb Spasticity

The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 33) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.
The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGi) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4 = very marked worsening to +4 = very marked improvement. Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 34).

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

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

* Significantly different from placebo (p<0.05)

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

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

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

14.5 Cervical Dystonia

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=82)</th>
<th>BOTOX (N=88)</th>
<th>95% CI on Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in CDSS at Week 6</td>
<td>-0.3</td>
<td>-1.3</td>
<td>(-2.3, 0.3)</td>
</tr>
<tr>
<td>% Patients with Any Improvement on Physician Global Assessment</td>
<td>31%</td>
<td>51%</td>
<td>(5%, 34%)</td>
</tr>
<tr>
<td>Pain Intensity Baseline</td>
<td>1.8</td>
<td>1.8</td>
<td></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>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.
In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 36. The total dose and muscles selected were tailored to meet individual patient needs.

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

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Number of Patients Treated in This Muscle (N=88)</th>
<th>Mean % Dose per Muscle</th>
<th>Mid-Range of % Dose per Muscle*</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 = "unarmour sweating is noticeable and never interferes with my daily activities"; 4 = "underarm sweating is intolerable and always interferes with my daily activities." A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

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

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

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group (p<0.001), but was not significantly different between the two BOTOX doses (see Table 37).

### Table 37: Study 1 - Study Outcomes

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

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

### 14.7 Blepharospasm

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

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

### 14.8 Strabismus

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

### 16 HOW SUPPLIED/STORAGE AND HANDLING

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

- 100 Units: NDC 0023-1145-01
- 200 Units: NDC 0023-3921-02

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

### Storage

Unopened vials of BOTOX should be stored in a refrigerator (2° to 8°C) for up to 36 months. Do not use after the expiration date on the vial. Administer BOTOX within 24 hours of reconstitution; during this period reconstituted BOTOX should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX should be clear, colorless, and free of particulate matter.

### 17 PATIENT COUNSELING INFORMATION

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

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

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

**Voiding Symptoms after Bladder Injections**

After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.
**MEDICATION GUIDE**

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

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

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

- Problems breathing or swallowing
- Spread of toxin effects

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

1. **Problems swallowing, speaking, or breathing.** These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with BOTOX or BOTOX Cosmetic.
   - People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with BOTOX or BOTOX Cosmetic.
   - Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving BOTOX or BOTOX Cosmetic have the highest risk of getting these problems.

2. **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
   - loss of strength and muscle weakness all over the body
   - double vision
   - blurred vision and drooping eyelids
   - hoarseness or change or loss of voice (dysphonia)
   - trouble saying words clearly (dysarthria)
   - loss of bladder control
   - trouble breathing
   - trouble swallowing

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

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

What are BOTOX and BOTOX Cosmetic?

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

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

**BOTOX Cosmetic** 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.

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.
Who should not take BOTOX or BOTOX Cosmetic?

Do not take BOTOX or BOTOX Cosmetic if you:

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

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

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

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

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

Especially tell your doctor if you:

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

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

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

How should I take BOTOX or BOTOX Cosmetic?

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

What should I avoid while taking BOTOX or BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause loss of strength or general muscle weakness, 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

Revised: 01/2016
This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by: Allergan Pharmaceuticals Ireland
a subsidiary of: Allergan plc
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Irvine, CA 92612
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