BOTOX®
onabotulinumtoxinA injection

Product Monograph

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and 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 Indications, Limitations of Use, and additional Important Safety Information about BOTOX® throughout this booklet.

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide, or visit https://www.rxabbvie.com/pdf/botox_pi.pdf

Committed to pursuing indications in diverse areas to help address patient needs

Overactive Bladder (2013)
BOTOX® for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Adult Detrusor Overactivity Associated With a Neurologic Condition (2011)
BOTOX® is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Pediatric Detrusor Overactivity Associated With a Neurologic Condition (2021)
BOTOX® is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

Chronic Migraine (2010)
BOTOX® is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥15 days per month with headache lasting 4 hours a day or longer).

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

Spasticity (2010, 2016, 2019, 2021*)
BOTOX® is indicated for the treatment of spasticity in patients 2 years of age and older.

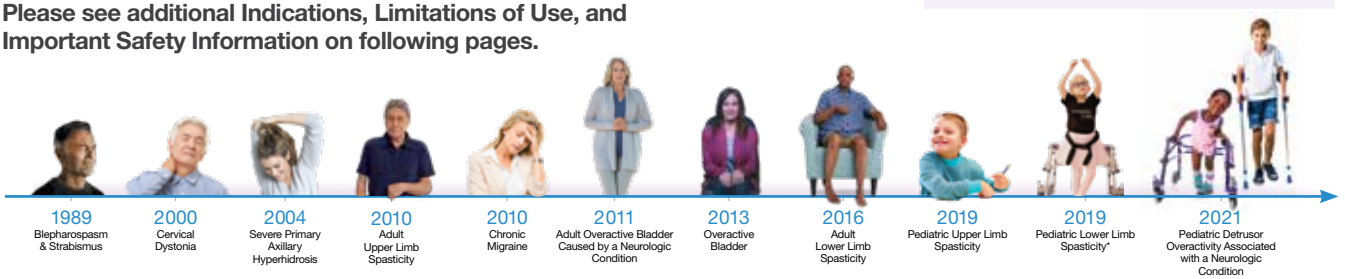
Limitations of Use
BOTOX® has not been shown to improve upper extremity functional abilities or range of motion at a joint affected by a fixed contracture.

Product packaging and handling
- Single-dose vial
- Unopened vials of BOTOX® should be stored in a refrigerator (2°C to 8°C) for up to 36 months; no need to freeze. Allergan hologram and the US license number (#1145) permit rapid authentication of BOTOX® product
- Supplied in secure vials with color-coded crimp and clear flip-top cap printed with “Allergan” and the Unit quantity
- The 2 different dosage vials can be easily distinguished: 200-Unit vial has an orange cap and 100-Unit vial has a purple cap

Please see additional Indications, Limitations of Use, and Important Safety Information on following pages.

Recommended total therapeutic doses for approved indications

	BOTOX®
Overactive bladder	100 Units
Adult detrusor overactivity associated with a neurologic condition	200 Units
Pediatric detrusor overactivity associated with a neurologic condition	200 Units (if patient’s body weight is ≥ 34 kg) 6 Units/kg (if patient’s body weight is < 34 kg) (See page 32, Table 16 for additional information)
Chronic Migraine	155 Units
Adult Upper Limb Spasticity	75 Units to 400 Units
Adult Lower Limb Spasticity	300 Units to 400 Units
Pediatric Upper Limb Spasticity	3 Units/kg to 6 Units/kg. The total dose of BOTOX® administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower
Pediatric Lower Limb Spasticity	4 Units/kg to 8 Units/kg. The total dose of BOTOX® administered per treatment session in the lower limb should not exceed 8 Units/kg or 300 Units, whichever is lower
Pediatric Spasticity	10 Units/kg body weight or 340 Units, whichever is lower
Severe primary axillary hyperhidrosis	50 Units/axilla
Cervical Dystonia	198 Units to 360 Units
Blepharospasm	1.25 Units to 2.5 Units/site
Strabismus	< 20 prism diopters: 1.25 Units to 2.5 Units/muscle 20 to 50 prism diopters: 2.5 Units to 5 Units/muscle



*BOTOX® was initially approved by the FDA for Pediatric Lower Limb Spasticity, excluding Spasticity caused by cerebral palsy in 2019. This marketing exclusivity was subsequently removed by the FDA in early 2020.

Contents

Introduction

BOTOX® is an injectable therapeutic agent that is used to treat select urologic, neurologic, dermatologic, and ophthalmic disorders as listed below and on the following page.

Indications for the use of BOTOX®

Adult 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 (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

BOTOX is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

Chronic Migraine

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

Limitations of Use

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

Spasticity

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

Limitations of Use

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

Please see additional Indications, Limitations of Use, and Important Safety Information about BOTOX® on following pages.

Indications for the use of BOTOX® (continued)

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.

Blepharospasm and Strabismus

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

Primary Axillary Hyperhidrosis

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

Limitations of Use

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.

IMPORTANT SAFETY INFORMATION (continued)
CONTRAINDICATIONS

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

BOTOX is contraindicated for intradetrusor injection in patients with a urinary tract infection, or in patients with urinary retention, or post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

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

Table 1. Extent of BOTOX® Approvals

Number of countries approved (as of March 2020)	≈100
Number of US approved indications	12

BOTOX® is one of the most widely researched medications in the world, with a proven history as a therapeutic agent (Data on file, AbbVie; BOTOX® Worldwide Marketing Authorization Status; BOTOX® Prescribing Information).

After 30 years of experience since FDA approval for Blepharospasm and Strabismus in 1989, BOTOX® is currently indicated for 40 disease states across ≈100 countries.

Please see full Indications and Limitations of Use on pages 4 and 5.

AbbVie is committed to educating patients and providers about BOTOX® treatment and the disorders it is used to treat. AbbVie provides literature and other educational information to specialists such as neurologists, urologists, physiatrists (physical medicine and rehabilitation specialists), dermatologists, and ophthalmologists—the physicians most likely to see and treat the disorders for which BOTOX® is used.

AbbVie sponsored training is available to physicians to illustrate BOTOX® injection protocols and to encourage appropriate administration. Through these materials and programs, AbbVie strives to promote early and accurate detection of the conditions for which it is used and to help physicians treat their patients.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS

Spread of Toxin Effect

See *Boxed Warning*.

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

Lack of Interchangeability Between Botulinum Toxin Products

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

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

Properties of BOTOX®

Units are not interchangeable with other neurotoxin products

BOTOX® is a biological product derived from a particular strain of the organism *Clostridium botulinum*.

The molecular weight of the botulinum neurotoxin protein complex in BOTOX® is a uniform ≈ 900 kilodaltons (kDa) (Lietzow et al, 2008). The complex undergoes strict purification processes to ensure a high-quality protein product. Specifically selected excipients (sodium chloride and human albumin) are added to these proteins to make the unique formulation of BOTOX®. The entire process of BOTOX® manufacturing exceeds the strict Good Manufacturing Process (GMP) standards.

As a result of the heterogeneity inherent in complex biological products, efficacy and safety data are required for each individual biological product seeking regulatory approval. That is, data sets generated with any 1 biological product cannot be used in support of another product seeking regulatory approval.

Furthermore, although the Units of some biological products are standardized, Units of botulinum neurotoxins are not. Thus, each botulinum neurotoxin product has its own Unit dosing that is not interchangeable with any others. Dosing of each product must be determined individually for each indication for safety requirements and clinical outcomes. The data reported in this monograph apply specifically to the product BOTOX® produced by AbbVie.

Another feature that distinguishes different botulinum neurotoxins is that each is required by the United States Food and Drug Administration (FDA) to have a distinct non-proprietary name. For BOTOX®, this name is onabotulinumtoxinA.

As new botulinum neurotoxin products are approved in the United States, they will be identifiable by their unique names—each of which will be associated with its own Unit dosing recommendations.

"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."

(BOTOX® Prescribing Information)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use

Initial U.S. Approval: 1989

WARNING: DISTANT SPREAD OF TOXIN EFFECT

See full prescribing information for complete boxed warning.

The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. (5.1)

(BOTOX® Prescribing Information, Page 1)

WARNINGS AND PRECAUTIONS

- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.1, 5.6)
- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.2, 11)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus. (5.13)

(BOTOX® Prescribing Information, Page 1)

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Toxin Effect

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

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

(BOTOX® Prescribing Information, Page 14)

Figure 1. Units of BOTOX® cannot be interchanged with those of any other botulinum toxin product, as per product labeling approved by the FDA.

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

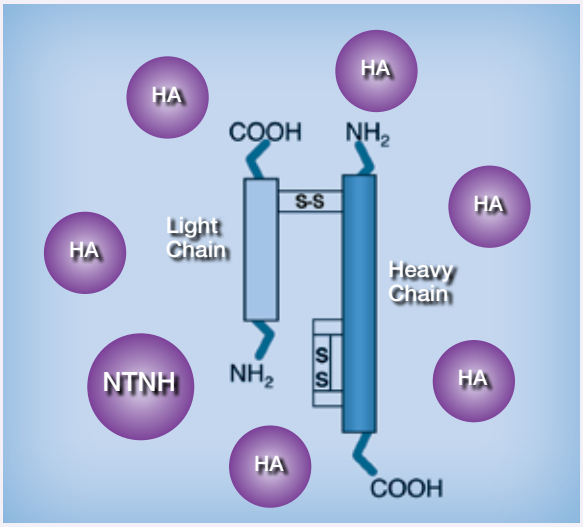
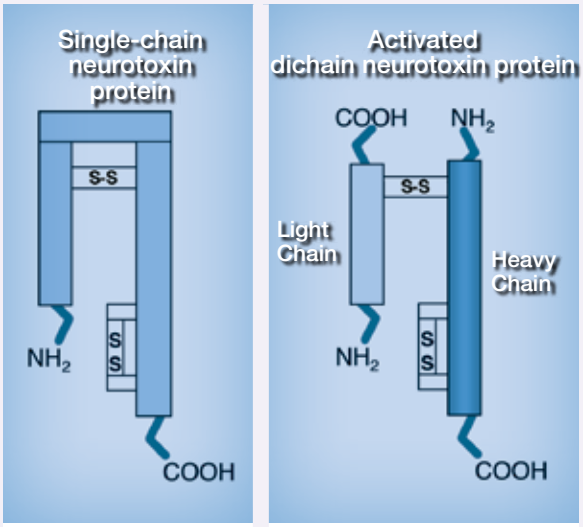


Figure 2. Structure of BOTOX® ≈ 900-kDa neurotoxin protein complex (schematic representation).



Abbreviations: COOH = carboxyl terminus; HA = hemagglutinin; NH_2 = amino terminus; NTNH = nontoxin, nonhemagglutinin; S-S = disulfide bond.

Figure 3. Diagram of botulinum neurotoxin single-chain protein and activated dichain protein.

Structure

Botulinum Toxin Type A is synthesized as a protein complex consisting of a 150-kDa neurotoxin as well as other associated proteins that vary depending on the particular strain of the *C botulinum* organism (Melling et al, 1988). BOTOX® neurotoxin contains the Botulinum Toxin Type A ≈ 900-kDa protein complex in its homogeneous form (Figure 2).

Botulinum Toxin Type A neurotoxin protein (150 kDa)

The 150-kDa Botulinum Toxin Type A protein is the portion of the complex responsible for the inhibition of exocytosis that reduces muscle spasms and severe sweating. Botulinum neurotoxins are synthesized by the bacteria as inactive single-chain proteins that have very little muscle-weakening activity (Wheeler and Smith, 2013; Simpson, 1981). In order to be activated, the single chain must be broken into 2 smaller fragments by proteolytic enzymes (Bonventre and Kempe, 1960) (Figure 3). This process is referred to as *nicking*. In nature, the Botulinum Toxin Type A molecule is most often found in its activated or nicked form (≈ 95%) (Wheeler and Smith, 2013).

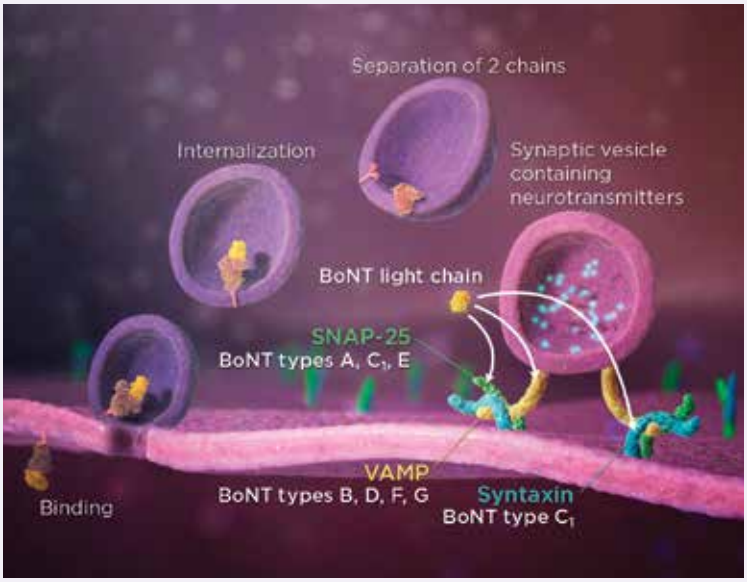
Additional neurotoxin complex proteins (750 kDa)

The other proteins in BOTOX® include hemagglutinin (HA) and nontoxin, nonhemagglutinin (NTNH) proteins. These nonneurotoxin proteins play an important role in stabilizing and protecting the 150-kDa neurotoxin protein from gastrointestinal degradation when ingested. However, when botulinum neurotoxin is directly injected into the target site and the gastrointestinal tract is bypassed, the clinical role of these nonneurotoxin proteins is unclear (Chen et al, 1998; Sharma and Singh, 1998).

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 preexisting 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.

Figure 4. Mechanism of action of botulinum neurotoxins. The ≈ 150-kDa botulinum neurotoxin protein binds to the nerve cell membrane. It is then internalized into the cell, where the light-chain portion (≈ 50 kDa) separates from the heavy-chain portion (≈ 100 kDa). The light chain translocates to the cytoplasm, where it cleaves 1 or more of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins needed for vesicular neurotransmitter release. Botulinum neurotoxin (BoNT) types A, C_1, and E cleave synaptosomal-associated protein 25 kDa (SNAP-25). BoNT types B, D, F, and G cleave vesicular-associated membrane protein (VAMP), also known as synaptobrevin. Type C_1 also cleaves syntaxin. Without intact SNARE proteins, vesicular neurotransmitter release is reduced.



Mechanism of action

The mechanism of action of Botulinum Toxin Type A was originally determined using tissues from experimental animals and cultured cells (Binz et al, 1994; Black and Dolly, 1986; Blasi et al, 1993).

BOTOX® is injected directly into muscles or the axillary skin surrounding autonomic glands. In these tissues, Botulinum Toxin Type A binds to acceptors on the terminals of acetylcholine-containing neurons (Wheeler and Smith, 2013) that innervate the muscles and sweat glands.

Botulinum Toxin Type A then enters the nerve ending, where it cleaves 1 of the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins. The SNARE complex is the apparatus responsible for vesicle docking and fusion that result in neuronal exocytosis of acetylcholine and many other neurotransmitters (Wheeler and Smith, 2013). Botulinum Toxin Type A cleaves a SNARE protein called synaptosomal-associated protein 25 kDa (SNAP-25) (Blasi et al, 1993).

The site at which Botulinum Toxin Type A cleaves SNAP-25 is unique to the A serotype. Botulinum neurotoxin serotypes C_1 and E also cleave SNAP-25, but at different sites than Type A (Binz et al, 1994; Foran et al, 2003; Schiavo et al, 1993a). Other botulinum neurotoxin serotypes (eg, types B, D, F, and G) cleave vesicle-associated membrane protein (VAMP, also known as synaptobrevin), another intracellular protein that is integral to SNARE-complex formation (Schiavo et al, 1992, 1993b; Yamasaki et al, 1994a, 1994b). Serotype C_1 also cleaves another protein called syntaxin (Foran et al, 2003).

As a result of this protein cleavage, acetylcholine release in the injected tissue is diminished (Polak et al, 1981). When injected intramuscularly at therapeutic doses, BOTOX® produces partial temporary chemical denervation of the muscle, resulting in a localized reduction in muscle activity. Following intradetrusor injection, BOTOX® affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. When injected intradermally, BOTOX® produces temporary chemical denervation of the sweat gland, resulting in local reduction in sweating. The mechanism of action of BOTOX® in Chronic Migraine is unknown.

Mechanism of action (continued)

The effects of botulinum neurotoxins are reversible, resulting in a return of neurotransmitter release over time. The reversal of botulinum toxin's effects has been primarily studied at the neuromuscular junction. Over time, the lack of acetylcholine release leads to the growth of new axonal sprouts. These sprouts may form neuromuscular junctions and begin to release acetylcholine, as noted in human tissues (Wheeler and Smith, 2013). Preclinical evidence in experimental animals suggests that the axonal sprouts eventually regress and the original neuromuscular junction is re-established (de Paiva et al, 1999), although additional studies are needed to verify that this also occurs in humans.

BOTOX® for injection is a sterile, vacuum-dried purified Botulinum Toxin Type A, produced from fermentation of Hall strain *Clostridium botulinum* Type A. 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 human albumin and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

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

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

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

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

Pulmonary Effects of BOTOX in Patients With Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated With a Neurologic Condition
Patients with compromised respiratory status treated with BOTOX for spasticity or detrusor overactivity associated with a neurologic condition should be monitored closely.

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.

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

Immunogenicity

All biological products carry some risk of antibody development, also referred to as an *immune response* or *immunogenicity* (BOTOX® Prescribing Information). The science of botulinum toxin suggests that antibodies form in 2 categories, classified as *neutralizing* or *nonneutralizing*. Antibodies that develop against the core toxin are considered neutralizing (Dressler and Hallett, 2006). These would be expected to inhibit the toxin from binding to the nerve terminal, preventing the toxin from entering the neuron and interfering with its biologic activity (Dolimbek et al, 2007). Antibodies that develop against the core toxin's surrounding proteins are considered nonneutralizing (Dressler and Hallett, 2006). These would not be expected to interfere with the core toxin's biologic activity.

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 dose given at the longest feasible intervals between injections.

The following paragraphs report the incidence of patients developing neutralizing antibodies in BOTOX® randomized, controlled trials across indications. In 954 patients receiving BOTOX® 100 Units in the overactive bladder studies, no patients with analyzed specimens developed the presence of neutralizing antibodies. In 260 patients receiving BOTOX® 150 Units in the same studies, 3 developed neutralizing antibodies after at least one 150-Unit dose. Response to subsequent BOTOX® treatment was not different following seroconversion in these 3 patients (BOTOX® Prescribing Information).

In detrusor overactivity associated with a neurologic condition, patients with analyzed specimens in the adult 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 (BOTOX® Prescribing Information).

In 99 pediatric patients who had a negative baseline result for binding antibodies or neutralizing antibodies and had at least one evaluable post-baseline value from one randomized double-blind study and one double-blind extension study, no patients developed neutralizing antibodies after receiving 50 Units to 200 Units of BOTOX®. In pivotal trials for Chronic Migraine in adults, none of the 406 patients with analyzed specimens showed the presence of neutralizing antibodies (BOTOX® Prescribing Information).

In pivotal trials for Adult Upper Limb Spasticity patients (N = 380), the immunogenicity rate was 0.5% (BOTOX® Prescribing Information). In pivotal trials for severe primary axillary hyperhidrosis inadequately managed with topical agents (N = 445), the neutralizing antibody formation rate was 0.2% (BOTOX® Prescribing Information). Based on a long-term, open-label study (average of 9 injection cycles), the incidence of immunogenicity with BOTOX® in the treatment of Cervical Dystonia is 1.2% (BOTOX® Prescribing Information), where 4 of 326 patients in this study demonstrated antibody formation. Three of these patients developed clinical resistance after subsequent treatment, and 1 patient continued to respond to therapy through the study conclusion.

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

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 in the BOTOX® Prescribing Information with the incidence of antibodies in other studies or to other products may be misleading.

BOTOX® development for therapeutic use

1977, 1989

In 1977, Botulinum Toxin Type A underwent its first testing in human volunteers, and that year the first 12 patients received Botulinum Toxin Type A injections for the investigational treatment of Strabismus (Brin and Blitzer, 2013).

In 1989, Botulinum Toxin Type A was approved by the FDA under the name *Oculinum* (this product was later renamed BOTOX®) for the treatment of Strabismus and Blepharospasm associated with dystonia (Brin and Blitzer, 2013).

2000

In December 2000, BOTOX® neurotoxin was approved by the FDA for the treatment of Cervical Dystonia in adults to reduce the severity of abnormal head position and associated neck pain.

2004

In 2004, BOTOX® was approved for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Limitations of Use
The safety and effectiveness of BOTOX® for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.

2010

In 2010, BOTOX® neurotoxin was approved for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow, wrist, and finger flexors (biceps brachii, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, and flexor digitorum sublimis).

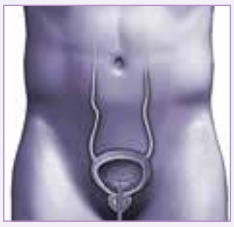
(See 2015 expansion of this Indication.)

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

Also in 2010, BOTOX® neurotoxin was approved for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

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

2011



In 2011, BOTOX® neurotoxin was approved for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Figure 5. History of BOTOX® development.

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

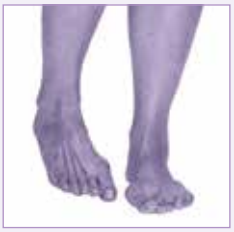
2013

In 2013, BOTOX® neurotoxin was approved 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.

2015

In 2015, the BOTOX® upper limb spasticity indication was expanded to include thumb flexors (adductor pollicis and flexor pollicis longus). At the same time, the recommended maximum cumulative dose in a 3-month period when treating adults for 1 or more indications was increased from 360 Units to 400 Units.

2016



In 2016, BOTOX® was approved 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).

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

2019

In 2019, BOTOX® was approved for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age.

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

Also in 2019, BOTOX® was approved for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age.*

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

2021

In 2021, BOTOX® was approved for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

Also in 2021, the BOTOX® label for Adult Spasticity was expanded to include 8 new muscles (brachialis, brachioradialis, pronator teres, pronator quadratus, lumbricals, interossei, flexor pollicis brevis, and opponens pollicis), as well as the use of ultrasound as a muscle localization technique.

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

Figure 5. History of BOTOX® development (continued).

*BOTOX® was initially approved by the FDA for Pediatric Lower Limb Spasticity, excluding Spasticity caused by cerebral palsy in 2019. This marketing exclusivity was subsequently removed by the FDA in early 2020.

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

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

Overactive Bladder

BOTOX® Indication

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

Description

Overactive bladder (OAB) is a urological condition. The hallmark symptom of OAB is urgency to urinate, but other symptoms are included in the diagnosis: urinary frequency, with or without urgency urinary incontinence. OAB is often associated with overactivity of the detrusor muscle (Gormley et al, 2014).

BOTOX® treatment

Study design and efficacy

Two double-blind, placebo-controlled, randomized, multicenter, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency. 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 (BOTOX® Prescribing Information).

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX® 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition (BOTOX® Prescribing Information). These primary and secondary variables are shown in Tables 2 and 3, and Figures 6 and 7.

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 adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units to 360 Units total dose) compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

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

Table 2. Baseline and Change From Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency, and Volume Voided per Micturition in Study OAB-1 (BOTOX® Prescribing Information)

	BOTOX® 100 Units (N = 278)	Placebo (N = 272)	Treatment Difference*	*P* Value*
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean baseline	5.5	5.1		
Mean change* at week 2	-2.6	-1.0	-1.6	
Mean change* at week 6	-2.8	-1.0	-1.8	
Mean change* at week 12†	-2.5	-0.9	-1.6 (-2.1, -1.2)	< 0.001
Daily Frequency of Micturition Episodes[b]				
Mean baseline	12.0	11.2		
Mean change‡ at week 12†	-1.9	-0.9	-1.0 (-1.5, -0.6)	< 0.001
Volume Voided per Micturition (mL)[b]				
Mean baseline	156	161		
Mean change‡ at week 12†	38	8	30 (17, 43)	< 0.001

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

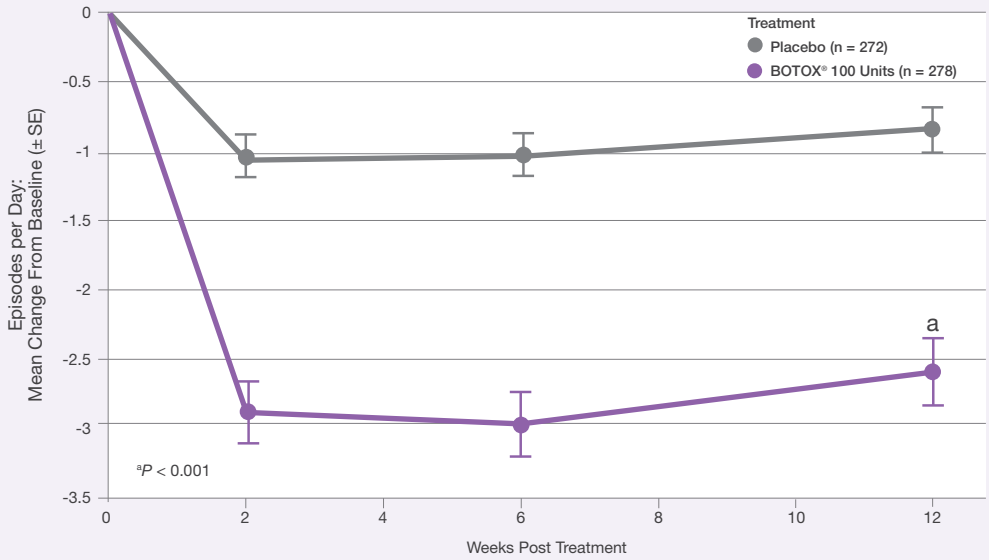
† Primary time point.

‡ 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.

[a] Primary variable.

[b] Secondary variable.

Figure 6. Mean change from baseline in daily frequency of urinary incontinence episodes following intradetrusor injection in Study OAB-1 (BOTOX® Prescribing Information).



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

Table 3. Baseline and Change From Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency, and Volume Voided per Micturition in Study OAB-2 (BOTOX® Prescribing Information)

	BOTOX® 100 Units (N = 275)	Placebo (N = 269)	Treatment Difference*	*P* Value*
Daily Frequency of Urinary Incontinence Episodes[a]				
Mean baseline	5.5	5.7		
Mean change* at week 2	-2.7	-1.1	-1.6	
Mean change* at week 6	-3.1	-1.3	-1.8	
Mean change* at week 12†	-3.0	-1.1	-1.9 (-2.5, -1.4)	< 0.001
Daily Frequency of Micturition Episodes[b]				
Mean baseline	12.0	11.8		
Mean change‡ at week 12†	-2.3	-0.6	-1.7 (-2.2, -1.3)	< 0.001
Volume Voided per Micturition (mL)[b]				
Mean baseline	144	153		
Mean change‡ at week 12†	40	10	31 (20, 41)	< 0.001

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

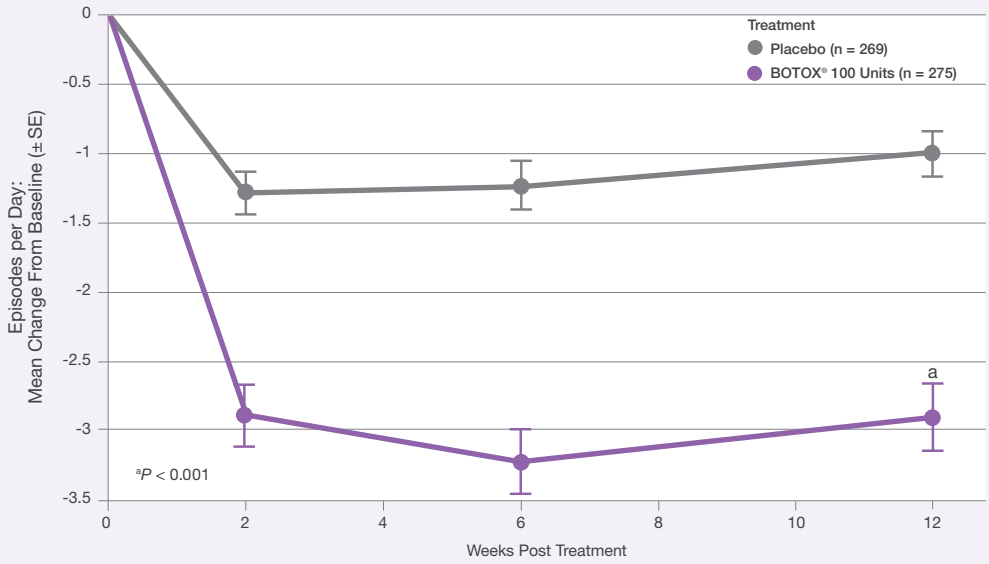
† Primary time point.

‡ 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.

[a] Primary variable.

[b] Secondary variable.

Figure 7. Mean change from baseline in daily frequency of urinary incontinence episodes following intradetrusor injection in Study OAB-2 (BOTOX® Prescribing Information).



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

Duration of response

The median duration of response in studies OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19 to 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 (BOTOX® Prescribing Information).

Urinary tract infections in patients with overactive bladder

BOTOX® increases the incidence of urinary tract infection (UTI). 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 (BOTOX® Prescribing Information).

Urinary retention in patients treated for overactive bladder

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 (BOTOX® Prescribing Information).

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 (BOTOX® Prescribing Information).

Clean intermittent catheterization

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 the table below. The duration of post-injection catheterization for those who developed urinary retention is also shown (BOTOX® Prescribing Information).

Table 4. Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB (BOTOX® Prescribing Information)

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

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

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

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

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

Adverse reactions in clinical trials

The following table 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 (BOTOX® Prescribing Information).

Table 5. 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

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

[a] 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 (eg, 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 the following table (BOTOX® Prescribing Information).

Table 6. Proportion of Patients Experiencing Urinary Tract Infection Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients With Diabetes		Patients Without Diabetes	
	BOTOX® 100 Units (N = 81) %	Placebo (N = 69) %	BOTOX® 100 Units (N = 526) %	Placebo (N = 516) %
Urinary tract infection (UTI)	31	12	26	10

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

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Urinary Retention in Adults Treated for Bladder Dysfunction
Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization posttreatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks posttreatment 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.

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

Pretreatment

Patients must not have a urinary tract infection at the time of treatment. Prophylactic antibiotics, (except aminoglycosides) should be administered 1 to 3 days pretreatment, on the treatment day, and 1 to 3 days post treatment to reduce the likelihood of procedure-related UTI (BOTOX® Prescribing Information).

Patients should discontinue antiplatelet therapy at least 3 days before the injection procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

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

The recommended dose is 100 Units of BOTOX® and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with 0.9% nonpreserved saline solution. Dispose of any unused saline (BOTOX® Prescribing Information).

Treatment

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

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

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

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 8). 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.

Post treatment

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 169 days [≈ 24 weeks]), but no sooner than 12 weeks from the prior bladder injection.

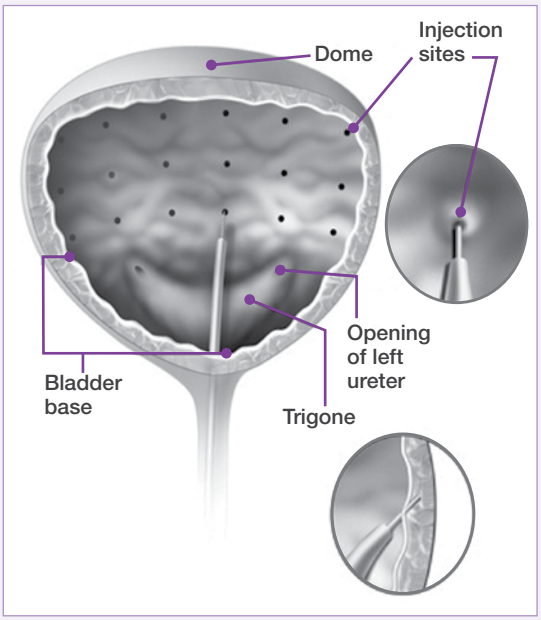


Figure 8. Injection pattern for intradetrusor injections for treatment of overactive bladder (BOTOX® Prescribing Information).

Adult Detrusor Overactivity Associated With a Neurologic Condition

BOTOX® Indication

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

Description

Neurologic conditions such as spinal cord injury and multiple sclerosis can cause urinary incontinence due to overactivity of the detrusor, a smooth muscle in the urinary bladder (Chancellor et al, 2006).

BOTOX® treatment

Study design and efficacy

BOTOX® was studied in 2 double-blind, placebo-controlled, randomized, multicenter clinical studies (NDO-1 and NDO-2) in patients with urinary incontinence (UI) due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (BOTOX® Prescribing Information).

A total of 691 SCI (T1 or below) or MS patients who had an inadequate response to, or were intolerant of, at least 1 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 were noted with BOTOX® 200 Units in the primary efficacy endpoint: change from baseline in weekly frequency of incontinence episodes at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction (secondary endpoints) were also observed. These primary and secondary endpoints are shown in Tables 7 and 8 and Figures 9 and 10 (BOTOX® Prescribing Information).

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

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Urinary Retention in Adults treated for Bladder Dysfunction (continued)
Overactive Bladder
In clinical trials, 6.5% of patients (36/552) initiated clean intermittent catheterization for urinary retention following treatment with BOTOX 100 Units, as compared to 0.4% of patients (2/542) treated with placebo. The median duration of catheterization for patients treated with BOTOX 100 Units was 63 days (minimum 1 day to maximum 214 days), as compared to a median duration of 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

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

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

Table 7. Baseline and Change From Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity, and Maximum Detrusor Pressure During First Involuntary Detrusor Contraction (cmH_20) in Study NDO-1 (BOTOX® Prescribing Information)

	BOTOX® 200 Units	Placebo	Treatment Difference*	*P* Value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	134	146		
Mean baseline	32.3	28.3		
Mean change* at week 2	-15.3	-10.0	-5.3	–
Mean change* at week 6†	-19.9	-10.6	-9.2 (-13.1, -5.3)	$P < 0.001$
Mean change* at week 12	-19.8	-8.8	-11.0	–
Maximum Cystometric Capacity (mL)[b]				
N	123	129		
Mean baseline	253.8	259.1		
Mean change* at week 6†	135.9	12.1	123.9 (89.1, 158.7)	$P < 0.001$
Maximum Detrusor Pressure During First Involuntary Detrusor Contraction (cmH_20)[b]				
N	41	103		
Mean baseline	63.1	57.4		
Mean change* at week 6†	-28.1	-3.7	-24.4	–

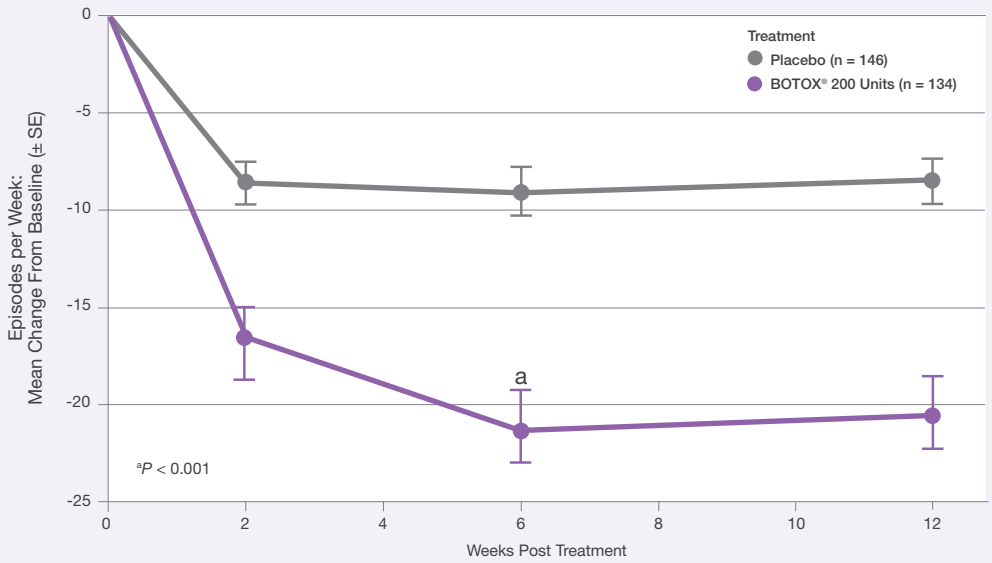
*LS mean change, treatment difference, and *P* value are based on an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (SCI or MS), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

† Primary time point.

[a] Primary endpoint.

[b] Secondary endpoint.

Figure 9. Mean change from baseline in weekly frequency of urinary incontinence episodes during treatment cycle 1 in study NDO-1 (BOTOX® Prescribing Information).



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

Table 8. Baseline and Change From Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity, and Maximum Detrusor Pressure During First Involuntary Detrusor Contraction (cmH_20) in Study NDO-2 (BOTOX® Prescribing Information)

	BOTOX® 200 Units	Placebo	Treatment Difference*	*P* Value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	91	91		
Mean baseline	32.7	36.8		
Mean change* at week 2	-18.0	-7.9	-10.1	–
Mean change* at week 6†	-19.6	-10.8	-8.8 (-14.5, -3.0)	$P = 0.003$
Mean change* at week 12	-19.6	-10.7	-8.9	–
Maximum Cystometric Capacity (mL)[b]				
N	88	85		
Mean baseline	239.6	253.8		
Mean change* at week 6†	150.8	2.8	148.0 (101.8, 194.2)	$P < 0.001$
Maximum Detrusor Pressure During First Involuntary Detrusor Contraction (cmH_20)[b]				
N	29	68		
Mean baseline	65.6	43.7		
Mean change* at week 6†	-28.7	2.1	-30.7	–

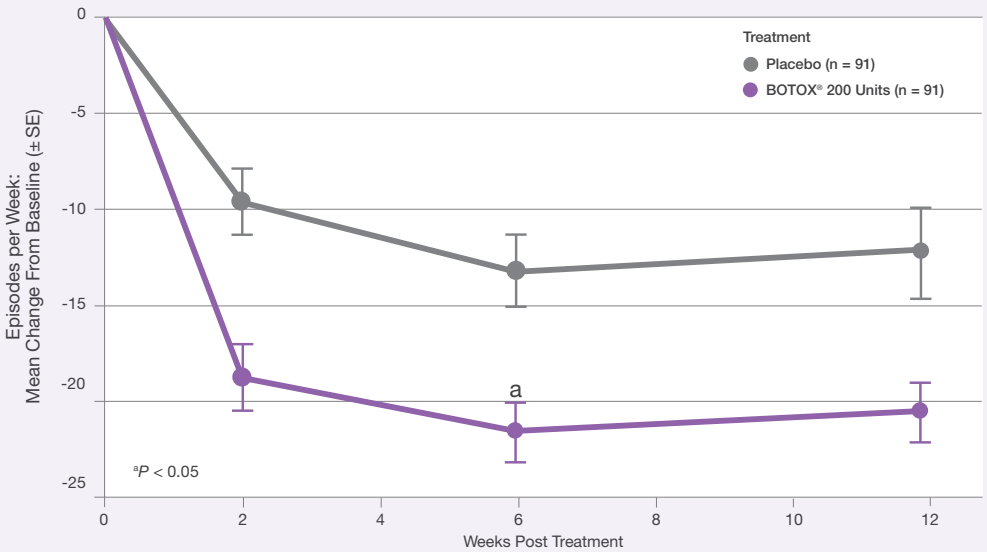
*LS mean change, treatment difference, and *P* value are based on an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (SCI or MS), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

† Primary time point.

[a] Primary endpoint.

[b] Secondary endpoint.

Figure 10. Mean change from baseline in weekly frequency of urinary incontinence episodes during treatment cycle 1 in study NDO-2 (BOTOX® Prescribing Information).



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

The median duration of response in Studies NDO-1 and NDO-2, based on patient qualification for re-treatment was 295 to 337 days (42-48 weeks) for the 200 Units dose group compared to 96 to 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).

BOTOX® was also studied in a placebo-controlled, double-blind, randomized, post-approval, 52-week study (NDO-3) of MS patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least 1 anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either BOTOX® 100 Units (n = 66) or placebo (n = 78) (BOTOX® Prescribing Information).

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 9 (BOTOX® Prescribing Information).

Table 9. Baseline and Change From Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure During First Involuntary Detrusor Contraction (cmH_2O) in Study NDO-3 (BOTOX® Prescribing Information)

	BOTOX® 100 Units	Placebo	Treatment Difference*	*P* Value*
Daily Frequency of Urinary Incontinence Episodes[a]				
N	66	78		
Mean baseline	4.2	4.3		
Mean change* at week 2	-2.9	-1.2	-1.7	–
Mean change* at week 6†	-3.4	-1.1	-2.3 (-3.0, -1.7)	$P < 0.001$
Mean change* at week 12	-2.7	-1.0	-1.8	–
Maximum Cystometric Capacity (mL)[b]				
N	62	72		
Mean baseline	248.9	245.5		
Mean change* at week 6†	134.4	3.5	130.9 (94.8, 167.0)	$P < 0.001$
Maximum Detrusor Pressure During First Involuntary Detrusor Contraction (cmH_20)[b]				
N	25	51		
Mean baseline	42.4	39.0		
Mean change* at week 6†	-19.2	2.7	-21.9 (-37.5, -6.3)	

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

† Primary time point.

[a] Primary endpoint.

[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 (BOTOX® Prescribing Information).

Autonomic dysreflexia and urinary retention

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

In 2 double-blind, placebo-controlled clinical trials (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 10. The duration of post-injection catheterization is also shown (BOTOX® Prescribing Information).

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 and diabetes mellitus. Depending on patient symptoms, catheterization should be instituted if PVR urine volume exceeds 200 mL and continued until PVR falls below 200 mL. Patients should be instructed to contact their physician if they experience difficulty in voiding, as catheterization may be required. Among patients not using CIC at baseline, those with MS were more likely to require CIC post injection than those with SCI (BOTOX® Prescribing Information).

Table 10. 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

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

Table 11. 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

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

A placebo-controlled, double-blind, post-approval, 52-week study with BOTOX® 100 Units (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 vs 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 (BOTOX® Prescribing Information).

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

Adverse reactions in clinical trials

The following table presents the most frequently reported adverse reactions in the two Phase 3 double-blind, placebo-controlled clinical trials (NDO-1 and NDO-2) within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX® 200 Units (BOTOX® Prescribing Information).

Table 12. Adverse Reactions Reported by ≥ 2% of BOTOX® Treated Patients and More Frequent Than in Placebo-Treated Patients Within the First 12 Weeks After Intradetrusor Injection in Double-Blind, Placebo-Controlled Clinical Trials (NDO-1 and NDO-2)

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

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

In the MS patients enrolled in the double-blind, placebo-controlled trials, the MS exacerbation annualized rate (eg, number of MS exacerbation reactions 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.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Urinary Retention in Adults Treated for Bladder Dysfunction (continued)
Adult Detrusor Overactivity Associated With a Neurologic Condition
In clinical trials, 30.6% of adult patients (33/108) who were not using CIC prior to injection required catheterization for urinary retention following treatment with BOTOX 200 Units, as compared to 6.7% of patients (7/104) treated with placebo. The median duration of postinjection catheterization for these patients treated with BOTOX 200 Units (n = 33) was 289 days (minimum 1 day to maximum 530 days), as compared to a median duration of 358 days (minimum 2 days to maximum 379 days) for patients receiving placebo (n = 7).

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

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.

The following table presents the most frequently reported adverse reactions in a placebo-controlled, double-blind, post-approval, 52-week study with BOTOX® 100 Units (NDO-3) conducted in MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least 1 anticholinergic agent and not catheterized at baseline (BOTOX® Prescribing Information).

Table 13. Adverse Reactions Reported in a Post-Approval Study (NDO-3) by > 2% of BOTOX® Treated Patients and More Frequent Than in Placebo-Treated Patients Within the First 12 Weeks After Intradetrusor Injection

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

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

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

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

A higher incidence of UTI was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than nondiabetics.

The incidence of UTI increased in patients who experienced a maximum PVR urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% vs 23%, respectively.

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

Pretreatment

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics (except aminoglycosides) should be administered 1 to 3 days pretreatment, on the treatment day, and 1 to 3 days post treatment to reduce the likelihood of procedure-related UTI (BOTOX® Prescribing Information).

Patients should discontinue antiplatelet therapy at least 3 days before the injection procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

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

The recommended dose is 200 Units of BOTOX® per treatment and should not be exceeded (BOTOX® Prescribing Information).

Treatment

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

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (≈ 6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 11). 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 (BOTOX® Prescribing Information).

Post treatment

After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post injection.

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

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

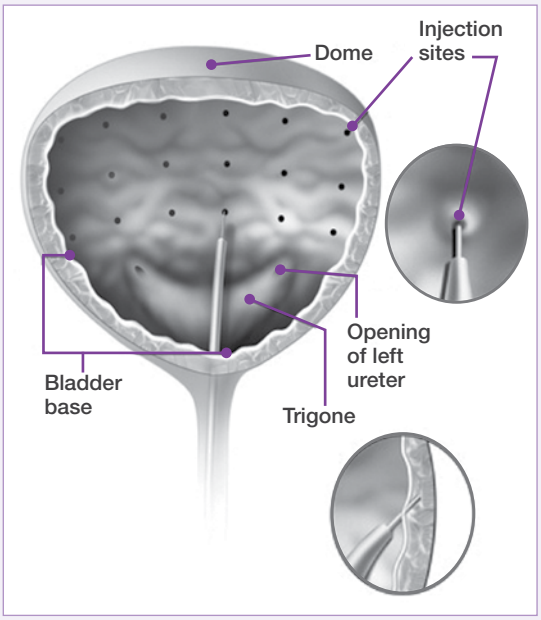


Figure 11. Injection pattern for intradetrusor injections for treatment of adult detrusor overactivity associated with a neurologic condition (BOTOX® Prescribing Information).

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

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

BOTOX® Indication

BOTOX® for injection is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

Description

Neurologic conditions such as spinal cord injury and spinal dysraphism (eg, spina bifida) in pediatric patients can cause overactivity of the detrusor. This can lead to urinary incontinence and elevated bladder pressures (Austin et al, 2021).

BOTOX® treatment

Study design and efficacy

Study 191622-120 (NCT01852045) was a multicenter, randomized, double-blind, parallel-group clinical study conducted in patients 5 to 17 years of age with urinary incontinence due to detrusor overactivity associated with a neurologic condition and using clean intermittent catheterization. A total of 113 patients with spinal dysraphism (n = 99), such as spina bifida, spinal cord injury (n = 13), and transverse myelitis (n = 1), who had an inadequate response to or were intolerant of at least one anticholinergic medication were enrolled. The median age was 11 years (range: 5 to 17 years); 49% were female; 75% were White, 10% were Black. These patients were randomized to BOTOX® 50 Units (n = 38), 100 Units (n = 45), or 200 Units (n = 30), not to exceed 6 Units/kg body weight. Patients receiving less than the randomized dose due to the 6 Units/kg maximum were assigned to the nearest dose group for analysis. Prior to treatment administration, patients received anesthesia based on age and local site practice. One hundred and nine patients (97.3%) received general anesthesia or conscious sedation, and 3 patients (2.7%) received local anesthesia (BOTOX® Prescribing Information).

*Detrusor pressure.

†Involuntary detrusor contraction.

The study results demonstrated within-group improvements in the primary efficacy variable of change from baseline in daytime urinary incontinence episodes (normalized to 12 hours) at the primary efficacy time point (week 6) for all 3 BOTOX® treatment groups. Additional benefits were seen with BOTOX® 200 Units for measures related to reducing maximum bladder pressure when compared to 50 Units. The decrease in maximum detrusor pressure (MDP) during the storage phase (MDP defined as the highest value in the Pdet* channel during the storage phase [eg, the greater of the following: the maximum Pdet during the highest amplitude IDC,† the maximum Pdet during a terminal detrusor contraction, the Pdet at the end of filling, or the highest Pdet at any other time during the storage phase]) for BOTOX® 200 Units at week 6 was greater than the decrease observed for 50 Units. Within-group improvements for the primary and secondary endpoints for the 200 Units dose group are shown in Table 14.

The efficacy of BOTOX® 6 Units/kg for pediatric patients with NDO weighing less than 34 kg was comparable to that of BOTOX® 200 Units (BOTOX® Prescribing Information).

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

Table 14. Baseline and Change From Baseline in Daily Daytime Frequency of Urinary Incontinence Episodes, Urine Volume at First Morning Catheterization, Maximum Detrusor Pressure During the Storage Phase (cmH_2O), and Maximum Cystometric Capacity (mL) in Study 191622-120 (BOTOX® Prescribing Information)

	BOTOX® 200 Units N = 30
Daily Average Frequency of Daytime Urinary Incontinence Episodes[a]	
Mean baseline	3.7
Mean change* at week 2 (95% CI)	-1.1 (-1.7, -0.6)
Mean change* at week 6† (95% CI)	-1.3 (-1.8, -0.9)
Mean change* at week 12 (95% CI)	-0.9 (-1.5, -0.4)
Urine Volume at First Morning Catheterization (mL)[b]	
Mean baseline	187.7
Mean change* at week 2 (95% CI)	63.2 (27.9, 98.6)
Mean change* at week 6† (95% CI)	87.5 (52.1, 122.8)
Mean change* at week 12 (95% CI)	45.2 (10.0, 80.5)
Maximum Detrusor Pressure (PdetMax) During the Storage Phase (cmH_20)[b]	
Mean baseline	56.7
Mean change* at week 6† (95% CI)	-27.3 (-36.4, -18.2)
Maximum Cystometric Capacity (mL) (MCC)[b]	
Mean baseline	202.3
Mean change* at week 6† (95% CI)	63.6 (29.0, 98.1)

CI = confidence interval.

*LS mean change and 95% CI are based on an ANCOVA model with baseline value as covariate and treatment group, age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (≤ 6 or > 6), and anticholinergic therapy (yes/no) at baseline as factors.

†Primary time point.

[a]Primary endpoint.

[b]Secondary endpoint.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Adult Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions within 12 weeks of BOTOX injection for detrusor overactivity associated with a neurologic condition include UTI (BOTOX 24%, placebo 17%); urinary retention (BOTOX 17%, placebo 3%); and hematuria (BOTOX 4%, placebo 3%).

The following adverse event rates were reported at any time following initial injection and prior to reinjection or study exit (median duration of 44 weeks of exposure): UTIs (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

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

Duration of response

The median duration of response in this study, based on patient qualification for re-treatment, was 207 days (30 weeks) for the BOTOX® 200 Units dose group. To qualify for re-treatment, patients must have reported at least 2 urinary incontinence episodes over 2 days and at least 12 weeks have passed since the prior bladder injection (BOTOX® Prescribing Information).

Adverse reactions in clinical trial

The following table presents the most frequently reported adverse reactions in Study 191622-120, a double-blind, parallel-group study conducted in pediatric patients with detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least 1 anticholinergic agent and were using clean intermittent catheterization at baseline (BOTOX® Prescribing Information).

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

The most common adverse reactions in patients who received BOTOX® 6 Units/kg and less than a total dose of 200 Units in Study 191622-120 were urinary tract infection (UTI), bacteriuria and hematuria (BOTOX® Prescribing Information).

Table 15. Adverse Reactions Reported by ≥ 3% of BOTOX® Treated Pediatric Patients Within the First 12 Weeks After Intradetrusor Injection, Study 191622-120

Adverse Reactions	BOTOX® 200 Unit (N = 30) %
Urinary tract infection	2 (7%)
Bacteriuria	6 (20%)
Leukocyturia	2 (7%)
Hematuria	1 (3%)

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions during the 12 weeks following BOTOX injection of 200 Units for pediatric detrusor overactivity associated with a neurologic condition include bacteriuria (20%), UTI (7%), leukocyturia (7%), and hematuria (3%).

The most common adverse reactions in patients who received BOTOX 6 Units/kg and less than a total dose of 200 Units were UTI, bacteriuria, and hematuria.

These patients were not adequately managed with at least one anticholinergic agent and were using clean intermittent catheterization at baseline.

Chronic Migraine

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

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

Pretreatment

Patients must not have a urinary tract infection (UTI) at the time of treatment. Oral prophylactic antibiotics, except aminoglycosides, should be administered 1 to 3 days pre-treatment, on the treatment day, and 1 to 3 days post-treatment to reduce the likelihood of procedure-related UTI. Alternatively, for patients receiving general anesthesia (or conscious sedation) for the treatment of detrusor overactivity associated with a neurologic condition, one dose of IV prophylactic antibiotics, except aminoglycosides, may be administered prior to treatment administration on the day of treatment.

Patients should discontinue antiplatelet therapy at least 3 days before the injection procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding (BOTOX® Prescribing Information).

Appropriate caution should be exercised when performing a cystoscopy.

- In patients 5 years to less than 12 years of age: Consider general anesthesia (or conscious sedation) prior to injection, per local site practice
- In patients 12 years of age or older: Consider an intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia prior to injection, per local site practice

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

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

Adult 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.

Pediatric Upper Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX in pediatric upper limb spasticity include upper respiratory tract infection (includes upper respiratory tract infection and viral upper respiratory tract infection), injection-site pain, nausea, constipation, rhinorrhea, nasal congestion, and seizure (includes seizure and partial seizure).

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

At a minimum, consider a diluted instillation of local anesthetic for all age groups. If a local anesthetic instillation is performed, drain and irrigate the bladder with sterile saline before injection (BOTOX® Prescribing Information).

If the patient's body weight is greater than or equal to 34 kg, the recommended dosage is 200 Units of BOTOX® per treatment administered as an intradetrusor injection after dilution (BOTOX® Prescribing Information):

- Reconstitute BOTOX® to result in 20 Units BOTOX®/mL in the vial(s):
  - BOTOX® 200-Unit vial: Add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently
  - BOTOX® 100-Unit vials: Add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to each of two 100-Unit vials of BOTOX® and mix the vials gently
- Draw 10 mL from the vial(s) into one 10-mL dosing syringe
- Use immediately after reconstitution in the syringe. Dispose of any unused saline

If the patient's body weight is less than 34 kg, the recommended dosage is 6 Units/kg body weight administered as a bladder injection after dilution (refer to Table 16) (BOTOX® Prescribing Information):

- Reconstitute BOTOX® to result in 20 Units BOTOX®/mL in the vial(s):
  - BOTOX® 200-Unit vial: Add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently
  - BOTOX® 100-Unit vial(s): Add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to one 100-Unit vial of BOTOX® (if final dose is less than or equal to 100 Units) or to each of two 100-Unit vials of BOTOX® (if final dose is greater than 100 Units) and mix the vial(s) gently
- Refer to Table 16 for dilution instructions (ie, the amount of reconstituted BOTOX® and additional diluent to draw into one 10-mL dosing syringe)
- Use BOTOX® immediately after reconstitution in the syringe. Dispose of any unused preservative-free 0.9% Sodium Chloride Injection, USP

Table 16. BOTOX® Dilution Instructions and Final Dosing for Patients With Body Weight < 34 kg (BOTOX® Prescribing Information)

Body Weight (kg)	Volume of Reconstituted Botox® and Diluent* (mL) to Draw Into Dosing Syringe to Achieve a Final Volume of 10 mL		Final Dose of Botox® in Dosing Syringe
	BOTOX® (mL)	Diluent* (mL)	
12 to less than 14	3.6	6.4	72 Units
14 to less than 16	4.2	5.8	84 Units
16 to less than 18	4.8	5.2	96 Units
18 to less than 20	5.4	4.6	108 Units
20 to less than 22	6	4	120 Units
22 to less than 24	6.6	3.4	132 Units
24 to less than 26	7.2	2.8	144 Units
26 to less than 28	7.8	2.2	156 Units
28 to less than 30	8.4	1.6	168 Units
30 to less than 32	9	1	180 Units
32 to less than 34	9.6	0.4	192 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP only.

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

Treatment

Reconstituted BOTOX® 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 (BOTOX® Prescribing Information).

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 12). 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 (BOTOX® Prescribing Information).

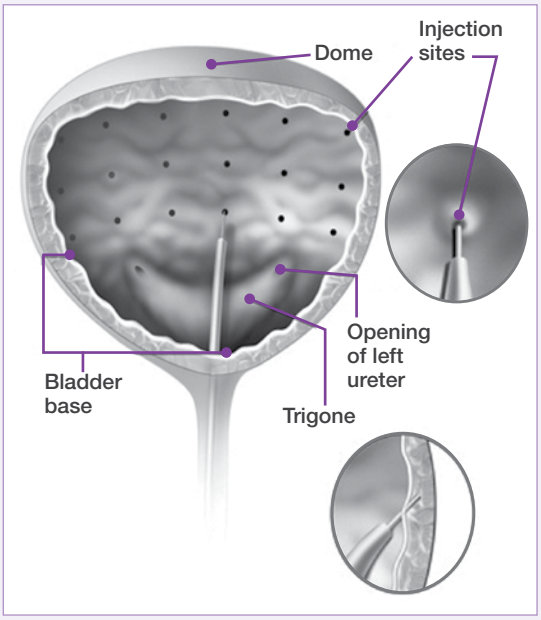


Figure 12. Injection pattern for intradetrusor injections for treatment of pediatric detrusor overactivity associated with a neurologic condition (BOTOX® Prescribing Information).

Post treatment

After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, parallel group clinical study was 207 days [30 weeks] for BOTOX® 200 Units), but no sooner than 12 weeks from the prior bladder injection (BOTOX® Prescribing Information).

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

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

Chronic Migraine

BOTOX® Indication

BOTOX® for injection is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Limitations of Use

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

Description

Chronic Migraine is defined as ≥ 15 headache days per month with headache lasting 4 hours a day or longer with at least 8 of the headache days being migraine (BOTOX® Prescribing Information; Lipton, 2011).

Migraines are headaches that typically last between 4 and 72 hours and may occur with or without aura; characteristics may include a pulsating quality, moderate or severe intensity, unilateral location, aggravation by routine physical activity, nausea and/or vomiting, photophobia, and phonophobia (IHS, 2018). Individuals with Chronic Migraine have a history of migraine (IHS, 2018).

Prevalence and underdiagnosis

A summary of 12 international population-based studies found that estimates of Chronic Migraine prevalence generally ranged from 1.4% to 2.2% (Natoli et al, 2010). Based on United States population data from 2010 and using the low end of that range, an estimated 3.3 million people in the United States have Chronic Migraine. Chronic Migraine affects approximately 10% of adults living with migraine disease (Natoli et al, 2010; CDC WONDER, 2010; Lipton et al, 2007).

According to survey data from 512 patients with Chronic Migraine, despite the high prevalence, only approximately 25% of patients who met criteria and sought evaluation from a healthcare professional were appropriately diagnosed with Chronic Migraine (Dodick et al, 2016).

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric lower limb spasticity include injection-site erythema, injection-site pain, oropharyngeal pain, ligament sprain, skin abrasion, and decreased appetite.

Cervical Dystonia

The most frequently reported adverse reactions following injection of BOTOX for cervical dystonia include dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

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

Evaluation

Headache pain is a subjective phenomenon that cannot be measured with a physical device and is difficult to assess in a clinical setting. Studies evaluating communication patterns between headache patients and physicians show that there is often misalignment about the frequency, severity, and impact of headache (Lipton et al, 2008). Furthermore, patients sometimes fail to communicate information about headache-related disability (Holmes et al, 2001). These challenges can lead to incomplete evaluation of a patient's condition and treatment progress.

Therefore, it is critical to have a well-established means of keeping track of headache-related symptoms/details. Accurate information is imperative to properly assess and diagnose a patient's headache condition, such as Chronic Migraine, and to determine the efficacy of treatment, especially with prophylactic treatments such as BOTOX®.

Recommended strategies for more productive communication include assessing headache-free days instead of migraine attacks and asking open-ended questions about headache impairment.

Headache diaries and patient questionnaires are also commonly used to evaluate Chronic Migraine patients (Aurora et al, 2010; Tfelt-Hansen et al, 2000). In these diaries, which may be in paper or electronic form, clinical trial subjects or patients can record their headache days, amount of pain medication taken, and other headache-related variables (IHS, 2018).

BOTOX® treatment

BOTOX® clinical efficacy

The efficacy and safety of BOTOX® for the treatment of Chronic Migraine patients was evaluated in 2 randomized, multicenter, 24-week, 2-injection-cycle, placebo-controlled, double-blind studies (N = 1384). Study 1 and Study 2 included adults with Chronic Migraine who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had ≥ 15 headache days lasting 4 hours or more, with at least 50% being migraine/probable migraine (BOTOX® Prescribing Information; Dodick et al, 2010).

In both studies, patients were randomized to receive placebo or 155-Unit BOTOX® injections every 12 weeks for the 2-treatment-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the studies (BOTOX® Prescribing Information).

Results of BOTOX® clinical studies in Chronic Migraine patients

BOTOX® treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (BOTOX® Prescribing Information).

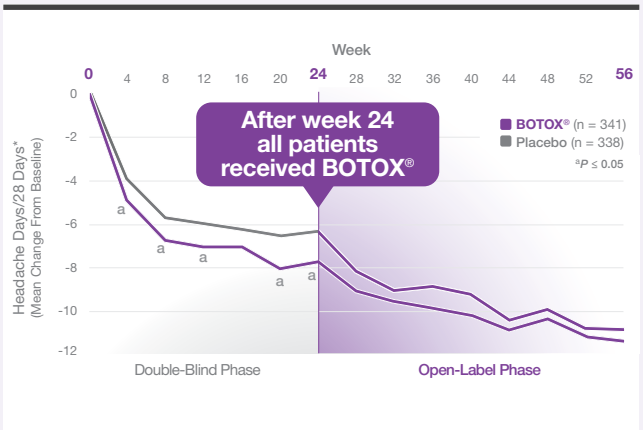
Table 17. Week 24 Key Efficacy Variables for Chronic Migraine Study 1 and Study 2 (BOTOX® Prescribing Information)

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

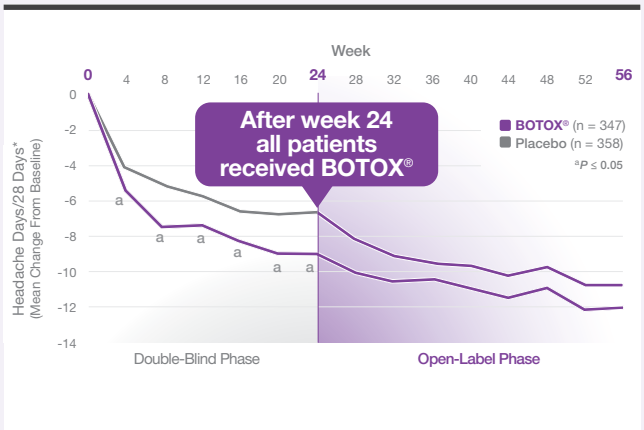
[a] Significantly different from placebo ($P \leq 0.05$).

Patients treated with BOTOX® had a significantly greater mean decrease from baseline in the frequency of headache days at most time points from week 4 to week 24 in Study 1 and all time points from week 4 to week 24 in Study 2, compared to placebo-treated patients (BOTOX® Prescribing Information; Data on file, AbbVie; PREEMPT 1 Final Report; Data on file, AbbVie; PREEMPT 2 Final Report).

Mean Change From Baseline in Number of Headache Days for Study 1



Mean Change From Baseline in Number of Headache Days for Study 2



*A headache day was defined as a calendar day per 28 days with ≥ 4 continuous hours of headache.

Figure 13. Results of BOTOX® clinical studies in Chronic Migraine patients.

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

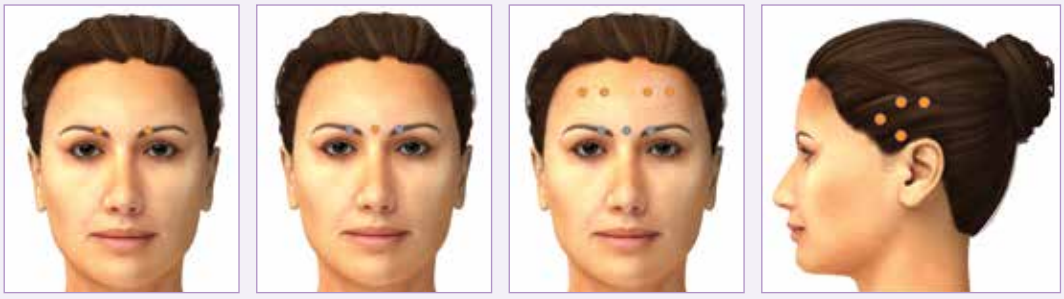
Injection paradigm and dosing

The recommended dose for treating Chronic Migraine is 155 Units administered intramuscularly (IM), 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 below. 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 section 2.2 of the full Prescribing Information for preparation and dilution techniques and additional dosing information). With the exception of the procerus muscle, which should be injected at 1 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.

In PREEMPT (**P**hase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy) trials, BOTOX® patients received 2 treatment cycles to determine the full effectiveness of treatment (as measured by the primary endpoint at 24 weeks). The recommended re-treatment schedule is every 12 weeks (BOTOX® Prescribing Information).

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

AbbVie offers peer-to-peer training opportunities for all experience levels, including information about patient assessment, functional anatomy, and injection technique. Speak to an AbbVie sales representative for additional details. Injection training videos are available at BOTOXAcademy.com.

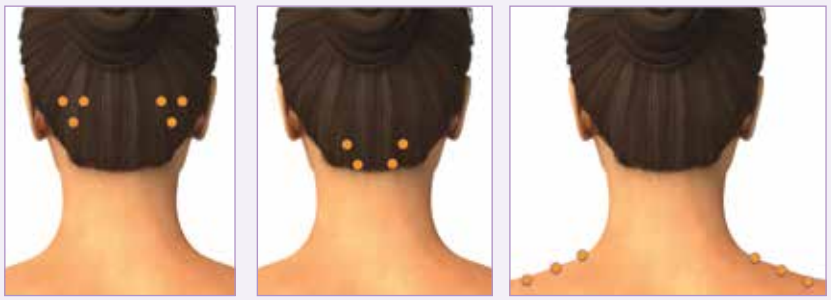


Corrugator
10 Units
divided in 2 sites

Procerus
5 Units
in 1 site

Frontalis
20 Units
divided in 4 sites

Temporalis
40 Units
divided in 8 sites



Occipitalis
30 Units
divided in 6 sites

Cervical paraspinals
20 Units
divided in 4 sites

Trapezius
30 Units
divided in 6 sites

Figure 14. Recommended BOTOX® dosing and injection site guidelines for Chronic Migraine patients.

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

Adverse reaction profile

The following table (Table 18) presents adverse reactions that were reported by ≥ 2% of BOTOX® treated patients and were more frequent than in placebo-treated patients in 2 Chronic Migraine double-blind, placebo-controlled clinical trials (BOTOX® Prescribing Information).

Table 18. Adverse Reactions in Chronic Migraine Clinical Trials

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

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

Adverse reaction profile (continued)

Discontinuations due to an adverse reaction were 4% in the BOTOX® group and 1% in the placebo group. Please see the adverse reactions table on page 38.

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

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Blepharospasm

The most frequently reported adverse reactions following injection of BOTOX for blepharospasm include ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Strabismus

The most frequently reported adverse events following injection of BOTOX for strabismus include ptosis (1% after inferior rectus injections, 16% after horizontal rectus injections, and 38% after superior rectus injections) and vertical deviation (17%).

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

Spasticity

BOTOX® Indication

Spasticity

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

Limitations of Use

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

Description

Spasticity is a condition of exaggerated stretch reflexes that are manifested clinically as muscle hypertonia and increased resistance to passive muscle stretch (Brown, 1994). This BOTOX® Product Monograph discusses spasticity in the upper and lower limbs of both adult and pediatric patients.

Measurement

The presence of spasticity is typically evaluated by physical examination. The physician may examine patient movements, palpate affected limbs, evaluate range of motion, test reflexes, and test for spastic catch, or the clasp-knife phenomenon, in upper limb spasticity (Mostoufi, 2005). The Ashworth Scale is a passive activity clinical scale used to rate muscle tone (Ashworth, 1964). 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 (eg, improvement in spasticity). The scale ranges from 0 (no increase in muscle tone) to 4 (affected parts rigid in flexion or extension).

Table 19. Ashworth Scale Score

Score	Severity	Definition
0	None	No increase in muscle tone
1	Mild	Slight increase in muscle tone, giving a “catch” when the limb was moved in flexion or extension
2	Moderate	More marked increase in muscle tone but affected limb is easily flexed
3	Severe	Considerable increase in tone—passive movement difficult
4	Very severe	Limb rigid in flexion or extension

The expanded Ashworth Scale (EAS) allows investigators to score half-point increments between each of the above categories. This is considered to allow more accurate recording of the patient’s condition. The modified Ashworth Scale (MAS) uses a similar scoring system as the Ashworth Scale.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Primary Axillary Hyperhidrosis
The most frequently reported adverse events (3%-10% of adult patients) following injection of BOTOX for severe primary axillary hyperhidrosis in double-blind studies include injection-site pain and hemorrhage, nonaxillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

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

Recommended dosing guidelines for BOTOX®

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 0.9% nonpreserved sterile saline (see Table 48 on page 90). 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 techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended.

Repeat BOTOX® treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX® and muscles to be injected. In separate adult upper and lower limb spasticity clinical trials, BOTOX® has been proven effective up to 400 Units. In Pediatric Spasticity clinical trials, BOTOX® has been proven effective up to 10 Units/kg body weight or 340 Units (whichever is lower) when treating both lower limbs or the upper and lower limbs in combination. As a result, BOTOX® dose may be tailored to the patient and desired clinical goal (BOTOX® Prescribing Information).

Doses of different botulinum neurotoxin products are not interchangeable. Doses provided in this monograph are specific to BOTOX®.

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

Adult Upper Limb Spasticity

Spasticity that affects the arms, elbows, wrists, fingers, or thumbs is referred to as *upper limb spasticity*. Upper limb spasticity can be seen in a number of conditions, including stroke, spinal cord injury, multiple sclerosis, traumatic brain injury, and adult cerebral palsy.

Pathology of Upper Limb Spasticity in Adults Is Similar Across Primary Conditions

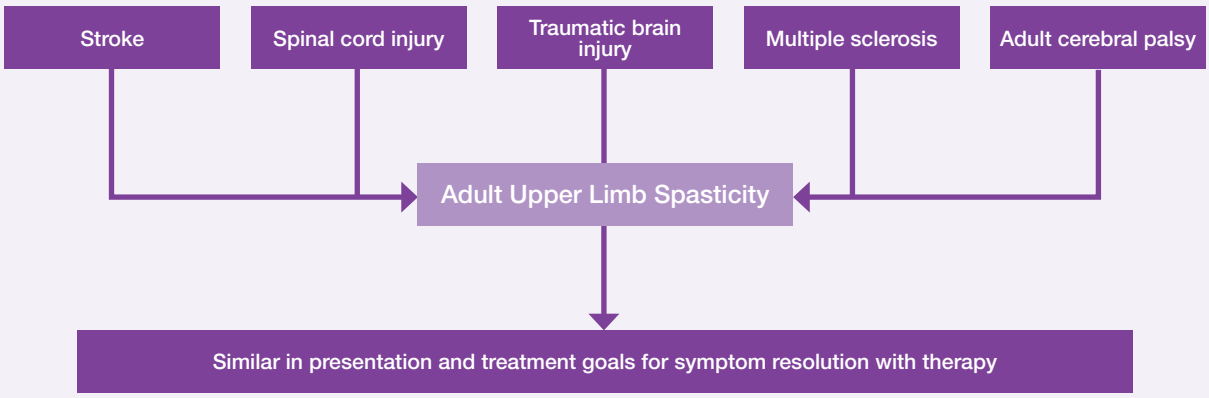


Figure 15. Conditions that can lead to upper limb spasticity in adults.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Postmarketing Experience
Adverse reactions that have been identified during postapproval use of BOTOX are discussed in greater detail in *Postmarketing Experience* (Section 6.3 of the Prescribing Information).

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.

The symptoms of upper limb spasticity are not evident immediately after a stroke, but rather develop after a delay of days, weeks, or months (O'Brien et al, 1996).

Untreated, spasticity can continue to worsen over time and may require early intervention. A clinical study found that 27% of post-stroke adult patients (N = 86) showed signs of spasticity at a median of 6 weeks (Wissel et al, 2010). A separate study showed that within 6 months of the stroke event, 52% of adult patients (N = 165) presented with a contracture in at least 1 joint (Kwah et al, 2012).

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

Upper limb spasticity is 1 of the delayed consequences of damage to the upper motor neuron pathways of the central nervous system (Sheean and McGuire, 2009). Patients may present with *generalized* symptoms, eg, increased muscle tightness/tonality that affects widespread regions of the body, or *focal* symptoms, eg, muscle tightness/tonality that affects 1 or more body parts in an isolated area (Elovic, 2011).

Upper limb spasticity can take a variety of different forms. Figure 16 shows some common clinical patterns of upper limb spasticity in adults. These abnormal postures are caused by marked muscle overactivity of the flexor muscles. Intrinsic plus hand (not shown in Figure 16) is characterized by flexion at the knuckle (metacarpophalangeal j oint) with extension at the proximal and distal interphalangeal joints, caused by imbalance between spastic intrinsic and weak extrinsic muscles of the hand.

Flexion of the wrist is caused by hypertonicity of the wrist flexor muscles, which seem to easily overpower their antagonists of wrist extension.

In those with **clenched fist,** the fingers are tightly flexed into the palm.

In those with **thumb in palm,** the thumb is bent in toward the palm.

The **flexed elbow** is bent into flexion, and this posture may dramatically worsen with ambulation, causing more severe angle flexion.

The **pronated forearm** appears to be much more common than the supinated forearm and impairs the ability to orient the hand.

Figure 16. Some common patterns of Adult Upper Limb Spasticity.

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

BOTOX® treatment

Muscle selection and dosing

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 20 and Figure 17) at a given treatment session.

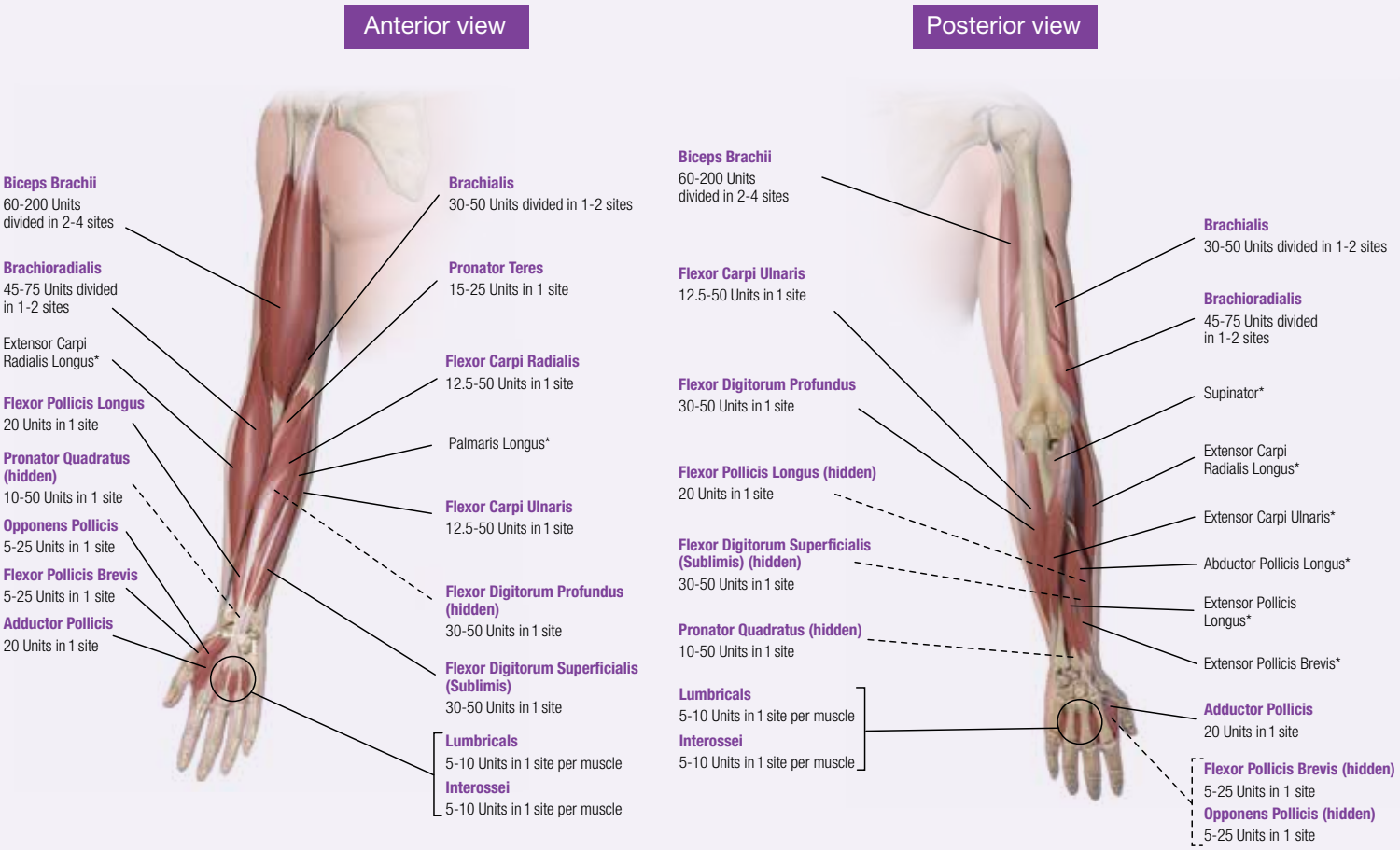
Table 20. Recommended BOTOX® Dose Ranges per Muscle for Adult Upper Limb Spasticity

Muscle	Total Dosage (Number of Sites)
Biceps brachii	60 Units to 200 Units divided in 2 to 4 sites
Brachialis	30 Units to 50 Units divided in 1 to 2 sites
Brachioradialis	45 Units to 75 Units divided in 1 to 2 sites
Pronator teres	15 Units to 25 Units in 1 site
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 digitorum sublimis	30 Units to 50 Units in 1 site
Flexor digitorum profundus	30 Units to 50 Units in 1 site
Flexor pollicis longus	20 Units in 1 site
Pronator quadratus	10 Units to 50 Units in 1 site
Flexor pollicis brevis	5 Units to 25 Units in 1 site
Opponens pollicis	5 Units to 25 Units in 1 site
Adductor pollicis	20 Units in 1 site
Lumbricals*	5 Units to 10 Units in 1 site per muscle
Interossei*	5 Units to 10 Units in 1 site per muscle

*When injecting both the lumbricals and interossei, consider limiting the combined total dose to 50 Units per hand.

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

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



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

Figure 17. Muscles approved for BOTOX® injection for Adult Upper Limb Spasticity (BOTOX® Prescribing Information).

INDICATIONS

Adult 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 (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

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

BOTOX® clinical efficacy

BOTOX® is a first-line option for treating Adult Upper Limb Spasticity. Its safety and efficacy were evaluated in 6 multicenter, randomized, placebo-controlled trials in post-stroke adult patients (BOTOX® Prescribing Information). In Study 1, 62 subjects received placebo and 64 subjects received a single treatment with BOTOX® at a total dose of 200 Units to 240 Units. In Study 2, 26 subjects received placebo and 65 subjects received 1 or 2 treatments with BOTOX® at doses of 90, 180, or 360 Units. In Study 3, 19 subjects received placebo and 69 subjects received a single treatment with BOTOX® at doses of 90, 180, or 360 Units. In Study 4, 83 patients received placebo and 87 patients received 20 Units of BOTOX® into the adductor pollicis and flexor pollicis longus (total BOTOX® dose = 40 Units in thumb muscles). In Study 5, patients received 15 Units (low dose; n = 14) or 20 Units (high dose; n = 43) of BOTOX® into the adductor pollicis and flexor pollicis longus under electromyographic (EMG) guidance (total BOTOX® low dose = 30 Units; total BOTOX® high dose = 40 Units), or placebo (low dose; n = 9; high dose; n = 23) (BOTOX® Prescribing Information). In Study 6, 63 patients received 240 Units of BOTOX® in the wrist and finger flexors plus either placebo or an additional 160 Units of BOTOX® (400 Units total; n = 61) in the elbow flexors (biceps brachii, brachioradialis, and brachialis).

Table 21. Study Methodology Overview (BOTOX® Prescribing Information; Data on file, AbbVie; Clinical Study Report 191622; Data on file, AbbVie; Clinical Study Report 133/134; Data on file, AbbVie; Clinical Study Report 418/422; Data on file, AbbVie; Clinical Study Report 112958; Data on file, AbbVie; Clinical Study Report 108509)

Adult ULS

	Number of Patients	Baseline Ashworth Score*	BOTOX® Dosage	Labeled Endpoints
Study 1	N = 126 BOTOX® (n = 64) Placebo (n = 62)	Wrist ≥ 3 Finger ≥ 2	200 Units to 240 Units	Median change from baseline in wrist flexor muscle tone (Ashworth Scale)†
Study 2	N = 91 BOTOX® (n = 65) Placebo (n = 26)	Elbow ≥ 2 Wrist ≥ 3	360 Units (n = 21) 180 Units (n = 23) 90 Units (n = 21)	Median change from baseline in wrist flexor muscle tone (expanded Ashworth Scale [EAS])†
Study 3	N = 88 BOTOX® (n = 69) Placebo (n = 19)	Elbow ≥ 2 Wrist and/or Finger ≥ 3	360 Units (n = 23) 180 Units (n = 23) 90 Units (n = 23)	Median change from baseline in elbow and wrist flexor muscle tone (EAS)‡
Study 4	N = 170 BOTOX® (n = 87) Placebo (n = 83)	Wrist ≥ 3 Finger ≥ 2	20 Units in the adductor pollicis 20 Units in the flexor pollicis longus	Median change from baseline in thumb flexor muscle tone (modified Ashworth Scale [MAS])§
Study 5	N = 109 BOTOX® (n = 72) Placebo (n = 37)	Wrist ≥ 3 Finger ≥ 2 Thumb ≥ 2	Low-dose group (n = 14) 15 Units into the adductor pollicis 15 Units into the flexor pollicis longus High-dose group (n = 43) 20 Units into the adductor pollicis 20 Units into the flexor pollicis longus	Median change from baseline in thumb flexor muscle tone (MAS‖ and Clinical Global Impression [CGI]§ scale)
Study 6	N = 124 BOTOX® (n = 61) BOTOX® + placebo (n = 63)	Elbow ≥ 3 Finger or Wrist ≥ 2	400 Units (n = 61) 240 Units (n = 63)	Mean change from baseline in elbow flexor muscle tone (MAS)†

Study participants received BOTOX® 240 Units in the wrist and finger flexors plus either placebo (n = 63) or an additional 160 Units of BOTOX® (400 Units total; n = 61) in the elbow flexors (biceps brachii, brachioradialis, and brachialis).

*Includes original, expanded, and modified Ashworth Scales.
†Primary endpoint at week 6.
‡Primary endpoint at week 4.
§Secondary endpoint at week 6.
‖Other endpoint at week 6.

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

Results of BOTOX® studied for Adult Upper Limb Spasticity

Table 22. Study 1: Primary and Key Secondary Endpoints by Muscle Group and at Week 6 (BOTOX® Prescribing Information)

	BOTOX® (n = 64)	Placebo (n = 62)
Median change from baseline in wrist flexor muscle tone on the Ashworth Scale*[,a]	-2.0‡	0.0
Median change from baseline in finger flexor muscle tone on the Ashworth Scale†[,b]	-1.0‡	0.0
Median change from baseline in thumb flexor muscle tone on the Ashworth Scale†[,c]	-1.0	-1.0
Median Physician Global Assessment of response to treatment†	2.0‡	0.0

*Primary endpoint at week 6.
†Secondary endpoints at week 6.
‡Significantly different from placebo ($P \leq 0.05$).
[a] BOTOX® injected into both the flexor carpi radialis and ulnaris muscles.
[b] BOTOX® injected into the flexor digitorum profundus and flexor digitorum sublimis muscles.
[c] BOTOX® injected into the adductor pollicis and flexor pollicis longus muscles.

Table 23. Study 2: Primary and Key Secondary Endpoints by Muscle Group and BOTOX® Dose at Week 6 (BOTOX® Prescribing Information)

	BOTOX® Low Dose (90 Units) (n = 21)	BOTOX® Mid Dose (180 Units) (n = 23)	BOTOX® High Dose (360 Units) (n = 21)	Placebo (n = 26)
Median change from baseline in wrist flexor muscle tone on the Ashworth Scale*[,a]	-1.5‡	-1.0‡	-1.5‡	-1.0
Median change from baseline in finger flexor muscle tone on the Ashworth Scale†[,b]	-0.5	-0.5	-1.0	-0.5
Median change from baseline in elbow flexor muscle tone on the Ashworth Scale†[,c]	-0.5	-1.0‡	-0.5[d]	-0.5
Median Physician Global Assessment of response to treatment	1.0‡	1.0‡	1.0‡	0.0

*Primary endpoint at week 6.
†Secondary endpoints at week 6.
‡Significantly different from placebo ($P \leq 0.05$).
[a] Total dose of BOTOX® injected into both the flexor carpi radialis and ulnaris muscles.
[b] Total dose of BOTOX® injected into the flexor digitorum profundus and flexor digitorum sublimis muscles.
[c] Dose of BOTOX® injected into biceps brachii muscle.
[d] $P = 0.053$

INDICATIONS (continued)

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

BOTOX is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

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

Table 24. Study 3: Primary and Key Secondary Endpoints by Muscle Group and BOTOX® Dose at Week 4 (BOTOX® Prescribing Information)

	BOTOX® Low Dose (90 Units) (n = 23)	BOTOX® Mid Dose (180 Units) (n = 21)	BOTOX® High Dose (360 Units) (n = 22)	Placebo (n = 19)
Median change from baseline in wrist flexor muscle tone on the Ashworth Scale*[,a]	-1.0	-1.0	-1.5‡	-0.5
Median change from baseline in finger flexor muscle tone on the Ashworth Scale†[,b]	-1.0	-1.0	-1.0‡	-0.5
Median change from baseline in elbow flexor muscle tone on the Ashworth Scale*[,c]	-0.5	-0.5	-1.0‡	-0.5

*Primary endpoint at week 4.
† Secondary endpoints at week 4.
‡ Significantly different from placebo ($P \leq 0.05$).
[a] Total dose of BOTOX® injected into both the flexor carpi radialis and ulnaris muscles.
[b] Total dose of BOTOX® injected into the flexor digitorum profundus and flexor digitorum sublimis muscles.
[c] Dose of BOTOX® injected into biceps brachii muscle.

Table 25. Study 4: Efficacy Endpoints for Thumb Flexors at Week 6 (BOTOX® Prescribing Information)

	BOTOX® (n = 66)	Placebo (n = 57)
Median change from baseline in thumb flexor muscle tone on the modified Ashworth Scale*[,a]	-1.0†	0.0
Median Physician Global Assessment of response to treatment*	2.0†	0.0

*Secondary endpoints at week 6.
† Significantly different from placebo ($P \leq 0.001$).
[a] BOTOX® injected into the adductor pollicis and flexor pollicis longus muscles.

INDICATIONS (continued)

Chronic Migraine

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

Limitations of Use

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

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

Table 26. Study 5: Efficacy Endpoints for Thumb Flexors at Week 6 (BOTOX® Prescribing Information)

	BOTOX® Low Dose (30 Units) (n = 14)	Placebo Low Dose (n = 9)	BOTOX® High Dose (40 Units) (n = 43)	Placebo High Dose (n = 23)
Median change from baseline in thumb flexor muscle tone on the modified Ashworth Scale*,[a]	-1.0	-1.0	-0.5†	0.0
Median change from baseline in Clinical Global Impression score by physician‡	1.0	0.0	2.0†	0.0

*Other endpoint at week 6.

†Significantly different from placebo ($P \leq 0.010$).

‡Secondary endpoint at week 6.

[a]BOTOX® injected into the adductor pollicis and flexor pollicis longus muscles.

Table 27. Study 6: Efficacy Endpoints for Elbow Flexors at Week 6 (BOTOX® Prescribing Information)

	BOTOX® 160 U (n = 61)	Placebo (n = 63)
Mean change from baseline in elbow flexor muscle tone on the modified Ashworth Scale at week 6	-1.09*	-0.71

*Nominal *P* value < 0.05.

INDICATIONS (continued)

Spasticity

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

Limitations of Use

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

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

BOTOX® adverse reactions in Adult Upper Limb Spasticity

Adverse reactions reported by ≥ 2% of BOTOX® treated patients and more frequent than in placebo-treated patients in adult spasticity double-blind, placebo-controlled clinical trials (BOTOX® Prescribing Information).

Table 28. Adverse Reactions in Adult Upper Limb Spasticity Trials

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

Twenty-two adult patients, enrolled in double-blind placebo-controlled studies, received 400 Units or higher of BOTOX® for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX® or higher for 4 consecutive treatments over approximately 1 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®.

INDICATIONS (continued)

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.

Blepharospasm and Strabismus

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

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

CASE STUDY: MK

"It's the little things that count. Before, my arm was stuck to my chest. Now it's a lot freer."

Initial assessment

Sought appointment after post-stroke team educated him on BOTOX® as a treatment for Adult Upper Limb Spasticity

Symptoms informing diagnosis

- Severe stiffness in upper arm
- Elbow bent with hand touching chest
- Concern for the burden his condition places on family caregiver

Treatment plan

BOTOX® as first-line treatment for Adult Upper Limb Spasticity, increased muscle tone in elbow and wrist

Four weeks after BOTOX® treatment

- Muscle stiffness reduced to moderate

Individual results may vary.

Figure 18. A post-stroke adult patient with upper limb spasticity.

CASE STUDY: CV

"When I first heard about BOTOX® I was really surprised and relieved that there was something out there that could help this."

Initial assessment

Referred by post-stroke physical therapist, who noticed spasticity in patient's left arm

Symptoms informing diagnosis

- Tense upper arm
- Increasing difficulty keeping hand in open position

Treatment plan

BOTOX® injections (with EMG guidance) as first-line treatment for Adult Upper Limb Spasticity, increased muscle tone in wrist and fingers

Four weeks after BOTOX® treatment

- Reduced muscle stiffness
- Able to use her good hand to open the fingers of her affected hand for cleaning

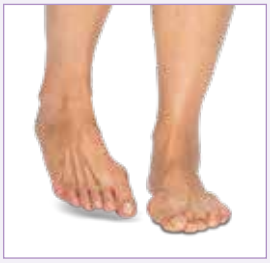
Individual results may vary.

Figure 19. A post-stroke adult patient with upper limb spasticity.

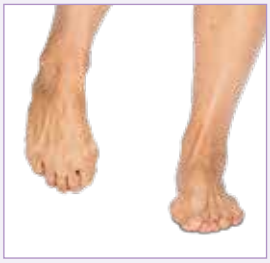
Adult Lower Limb Spasticity

Spasticity that affects the ankle and toes is referred to as *lower limb spasticity*. According to a market research study, over 70% of adult spasticity patients (n = 85) experience lower limb spasticity (LLS Impact Survey, 2014).

Lower limb spasticity can present in several different forms. Figure 20 shows some common clinical patterns seen in Adult Lower Limb Spasticity, which are caused by overactivity of the flexor muscles indicated.



Flexed ankle is caused by hypertonicity of the ankle flexors, including the gastrocnemius, soleus, and tibialis posterior.



Flexed toes are caused by hypertonicity of the toe flexors, including the flexor digitorum longus and flexor hallucis longus.

Figure 20. Presentation of Adult Lower Limb Spasticity.

BOTOX® treatment

Muscle selection and dosing

The recommended dose for treating Adult Lower Limb Spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor digitorum longus, and flexor hallucis longus) (see Table 29 and Figure 21) (BOTOX® Prescribing Information).

Table 29. BOTOX® Dosing by Muscle for Adult Lower Limb Spasticity

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

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

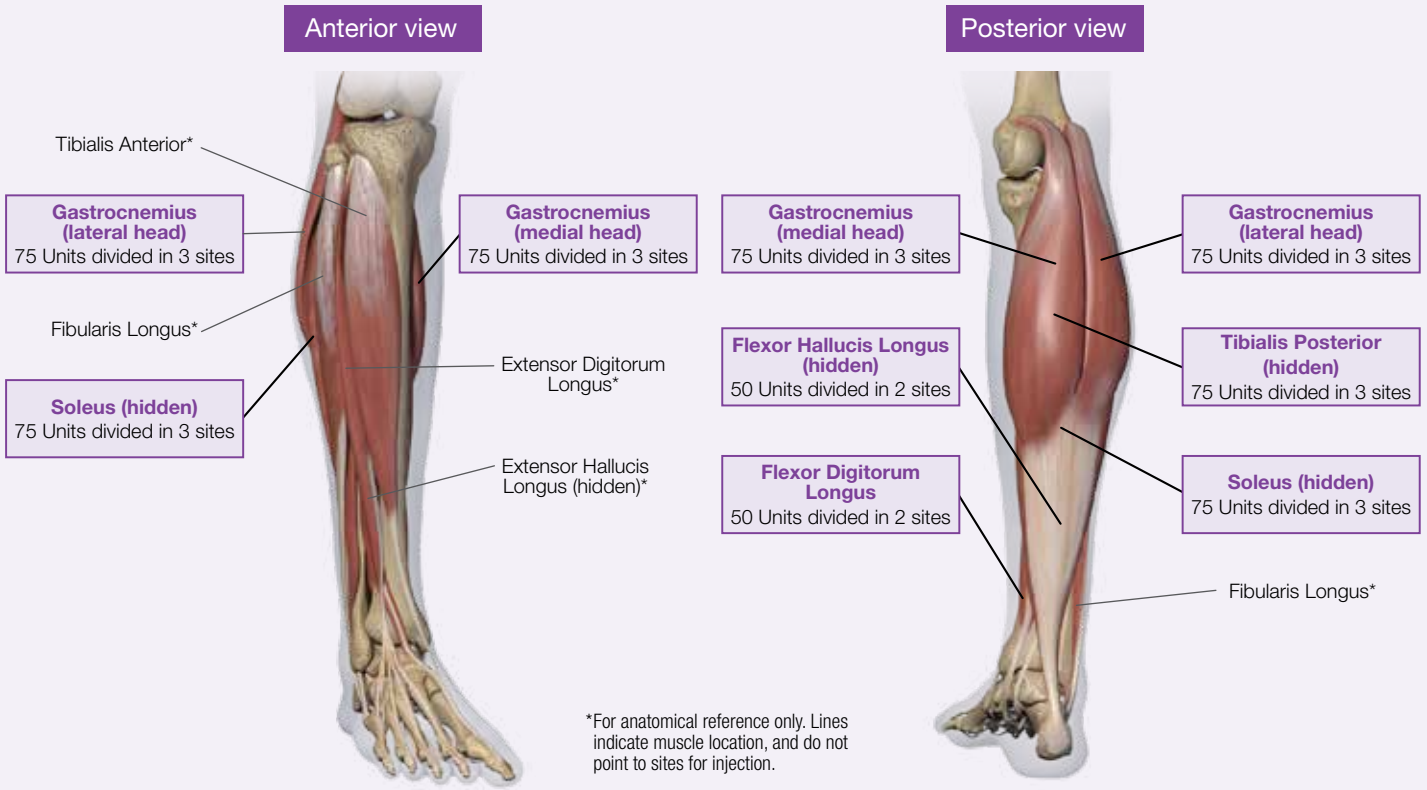


Figure 21. Muscles approved for BOTOX® injection in Adult Lower Limb Spasticity (BOTOX® Prescribing Information).

It is recommended that BOTOX® injections be divided across the 5 specific leg muscles as shown in the diagrams below (Figure 22).

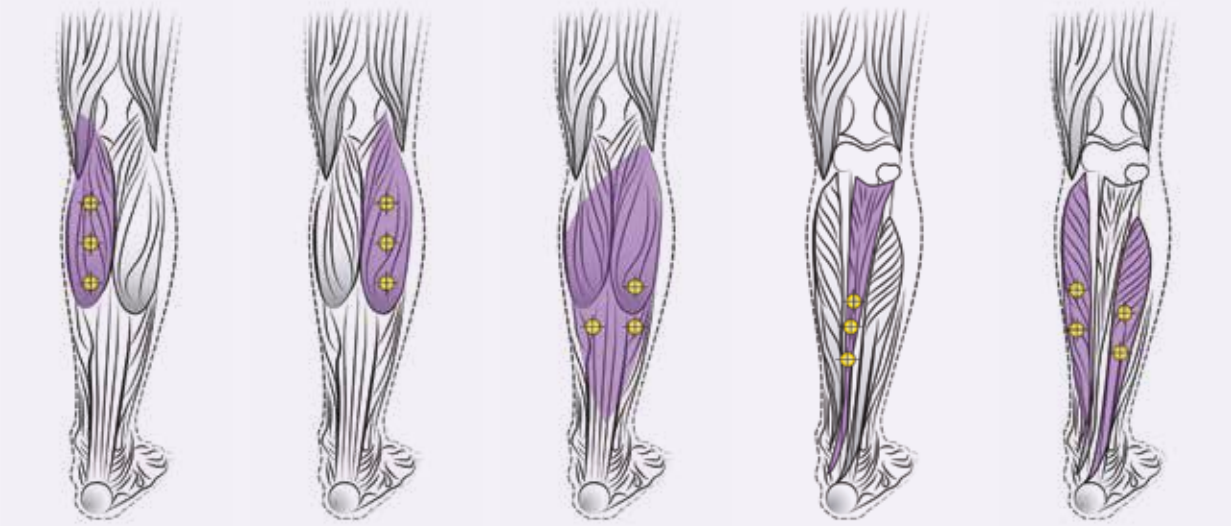


Figure 22. Injection sites for Adult Lower Limb Spasticity (BOTOX® Prescribing Information).

BOTOX® clinical efficacy

The efficacy and safety of BOTOX® for the treatment of Adult Lower Limb Spasticity were evaluated in a randomized, multicenter, double-blind, placebo-controlled study. This study included 468 post-stroke patients (233 BOTOX® and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score ≥ 3) who were at least 3 months post stroke. Patients were followed for 12 weeks (BOTOX® Prescribing Information).

Table 30. Study Methodology Overview (BOTOX® Prescribing Information)

Number of Patients	Time Since Stroke	BOTOX® Dosage	Co-primary Endpoints	Follow-up
N = 468 BOTOX® (n = 233) Placebo (n = 235)	≥ 3 months	300 Units to 400 Units	• Average of the change from baseline in modified Ashworth Scale ankle score at weeks 4 and 6 • Average of the Physician Global Assessment of response at weeks 4 and 6	12 weeks

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 with up to an additional 100 Units (400 Units total dose) (see Table 31). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections (BOTOX® Prescribing Information).

Table 31. Study Medication Dose and Injection Sites (BOTOX® Prescribing Information)

Muscles Injected	BOTOX® (Units)	Number of Injection Sites
Mandatory Ankle Muscles		
Gastrocnemius medial head	75	3
Gastrocnemius lateral head	75	3
Soleus	75	3
Tibialis posterior	75	3
Optional Muscles		
Flexor hallucis longus	50	2
Flexor digitorum longus	50	2
Flexor digitorum brevis*	25	1
Extensor hallucis*	25	1
Rectus femoris*	100	4

*Not approved for BOTOX® injection.

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

Results of BOTOX® studied for Adult Lower Limb Spasticity

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at weeks 4 and 6, and the average of the Physician Global Assessment of response at weeks 4 and 6.

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

Table 32. Co-primary Efficacy Endpoint Results (Intent-to-Treat Population)

Endpoints	BOTOX® 300 Units to 400 Units (n = 233)	Placebo (n = 235)
Mean change from baseline in ankle plantar flexors on the modified Ashworth Scale		
Week 4 and 6 average	-0.8*	-0.6
Mean Clinical Global Impression (CGI) score by investigator		
Week 4 and 6 average	-0.9*	0.7

*Significantly different from placebo ($P < 0.05$).

The CGI score 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.

INDICATIONS (continued)

Primary Axillary Hyperhidrosis

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

Limitations of Use

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.

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

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 23) and mean CGI scores by visit (see Figure 24) were observed at weeks 2, 4, and 6 for patients treated with BOTOX®.

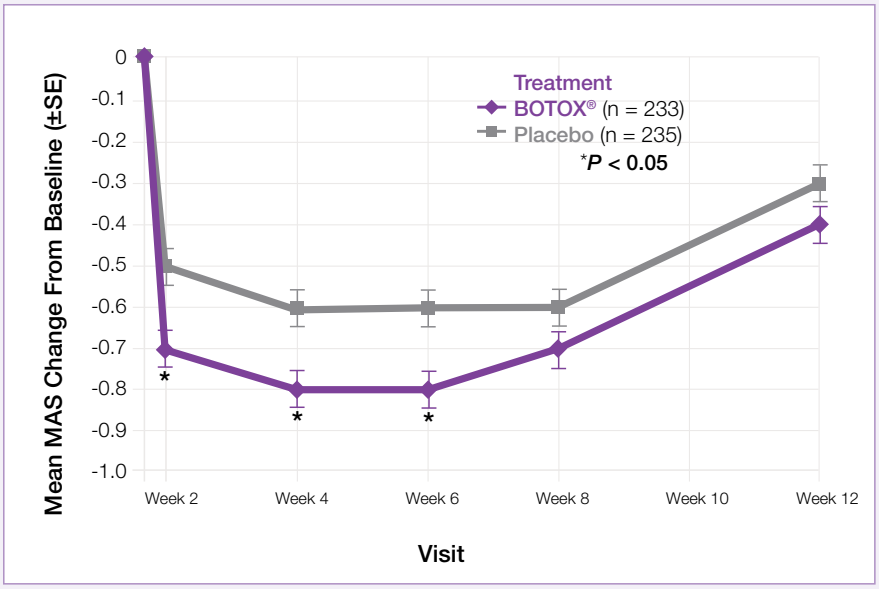


Figure 23. MAS ankle score—mean change from baseline by visit (BOTOX® Prescribing Information).

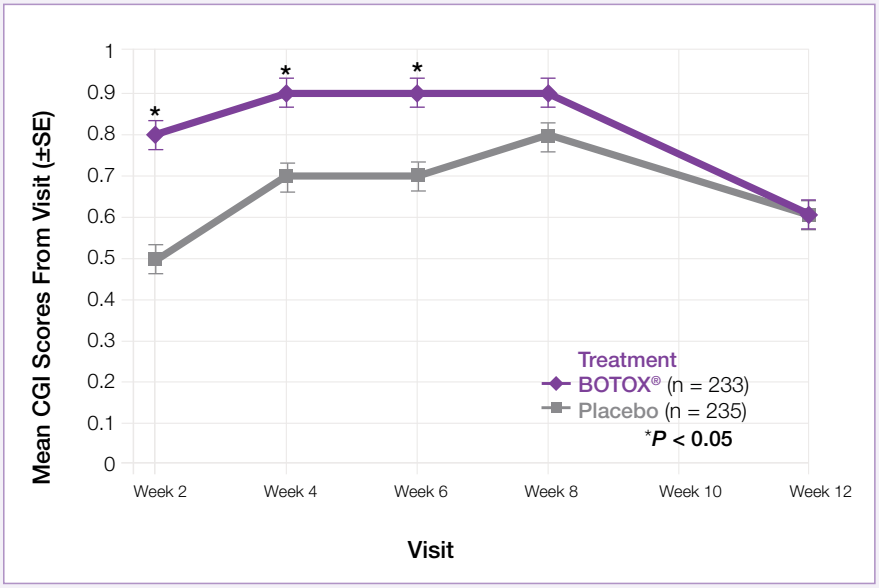


Figure 24. CGI—mean scores by visit (BOTOX® Prescribing Information).

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

BOTOX® adverse reactions in Adult Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® for Adult Lower Limb Spasticity appear in Table 33. Two hundred thirty-one patients enrolled in a double-blind, placebo-controlled clinical trial received 300 Units to 400 Units of BOTOX® and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

Table 33. Adverse Reactions Reported by ≥ 2% of BOTOX® Treated Patients and More Frequent Than in Placebo-Treated Patients in an Adult Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (BOTOX® Prescribing Information)

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

BOTOX is contraindicated for intradetrusor injection in patients with a urinary tract infection (UTI), or in patients with urinary retention or post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

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

Pediatric Upper Limb Spasticity

Upper limb spasticity can manifest in pediatric patients with a variety of neurologic conditions including cerebral palsy, ischemic stroke, traumatic brain injury, and spinal cord injury. Cerebral palsy is considered the most common cause of Pediatric Spasticity (Awaad et al, 2012).

Symptoms of Pediatric Spasticity vary among individuals and may change over time. Pediatric Spasticity is characterized by various clinical patterns, several of which are illustrated below (Figure 25), that can help with patient assessment.

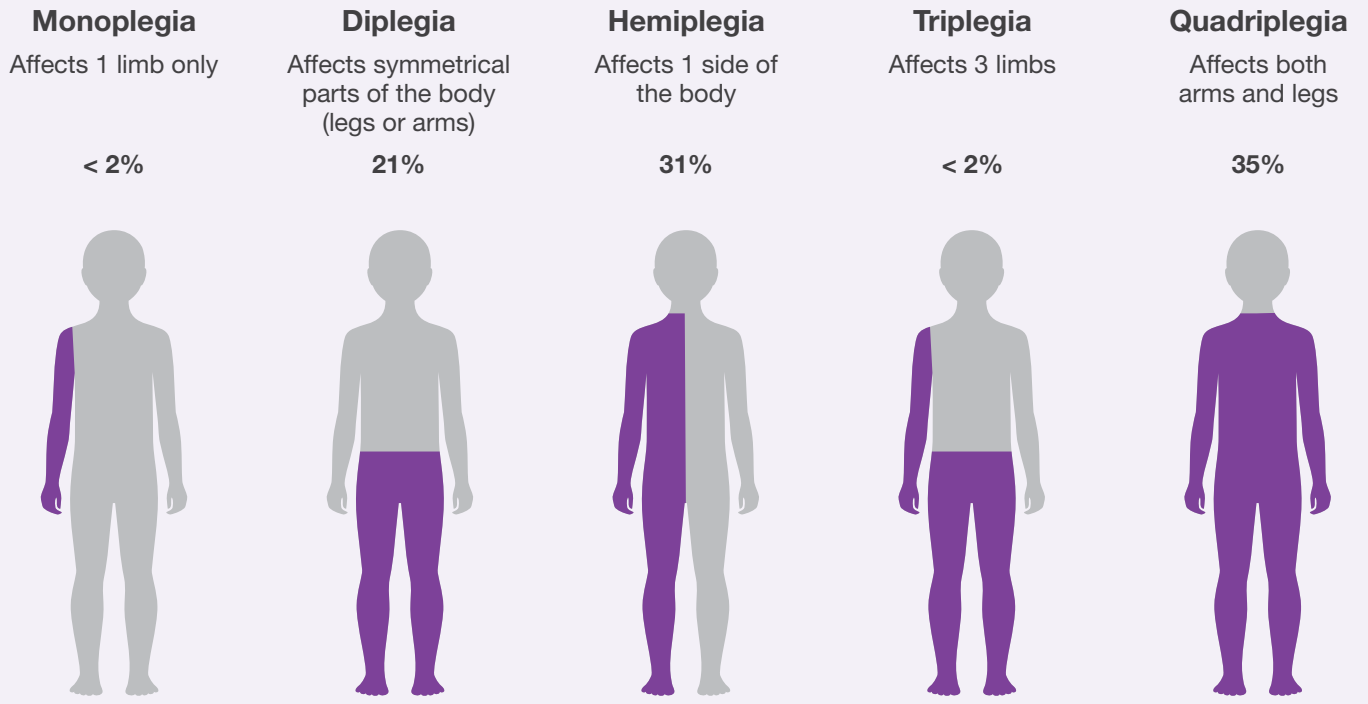


Figure 25. Clinical patterns of Pediatric Spasticity (Shevell et al, 2009).

Please note, in the BOTOX® clinical trial for Pediatric Upper Limb Spasticity, only monoplegic, hemiplegic, and triplegic patients were included.

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

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

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

BOTOX® treatment

Muscle selection and weight-based dosing

The recommended dose for treating Pediatric Upper Limb Spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles (see Table 34 and Figures 26 and 27) (BOTOX® Prescribing Information).

When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units in a 3-month interval. The total dose of BOTOX® administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower (BOTOX® Prescribing Information).

Additional *general* adult spasticity dosing information is also applicable to Pediatric Upper Limb Spasticity patients (see page 96) (BOTOX® Prescribing Information).

Table 34. BOTOX® Dosing by Muscle for Pediatric Upper Limb Spasticity (BOTOX® Prescribing Information)

	Muscle	BOTOX® Dose
Flexed elbow	Biceps brachii	1.5 Units/kg to 3 Units/kg divided in 4 sites
	Brachialis	1 Unit/kg to 2 Units/kg divided in 2 sites
	Brachioradialis	0.5 Unit/kg to 1 Unit/kg divided in 2 sites
Flexed wrist/fingers	Flexor carpi radialis	1 Unit/kg to 2 Units/kg divided in 2 sites
	Flexor carpi ulnaris	1 Unit/kg to 2 Units/kg divided in 2 sites
	Flexor digitorum profundus	0.5 Unit/kg to 1 Unit/kg divided in 2 sites
	Flexor digitorum superficialis (sublimis)	0.5 Unit/kg to 1 Unit/kg divided in 2 sites

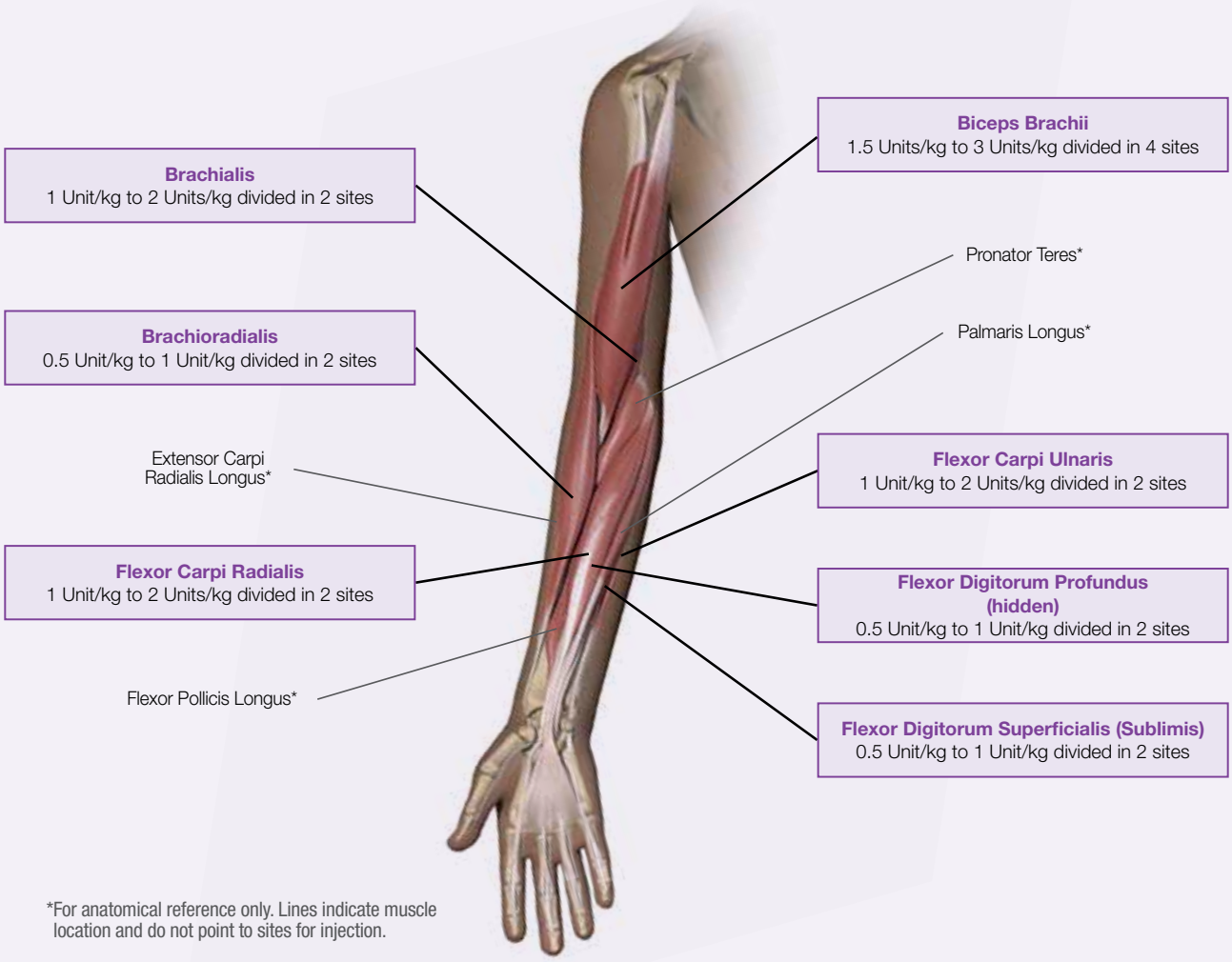


Figure 26. Muscles approved for BOTOX® injection in Pediatric Upper Limb Spasticity (BOTOX® Prescribing Information).

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 preexisting 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.

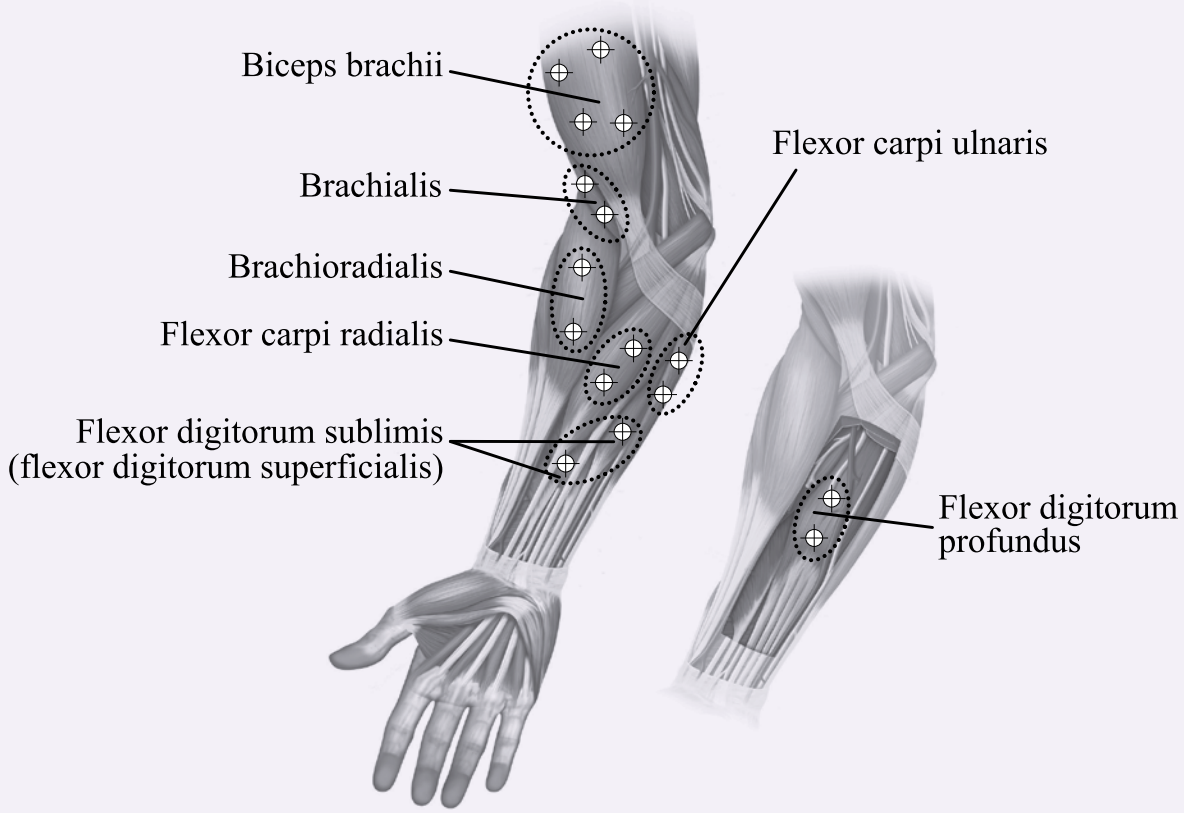


Figure 27. Injection sites for Pediatric Upper Limb Spasticity (BOTOX® Prescribing Information).

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

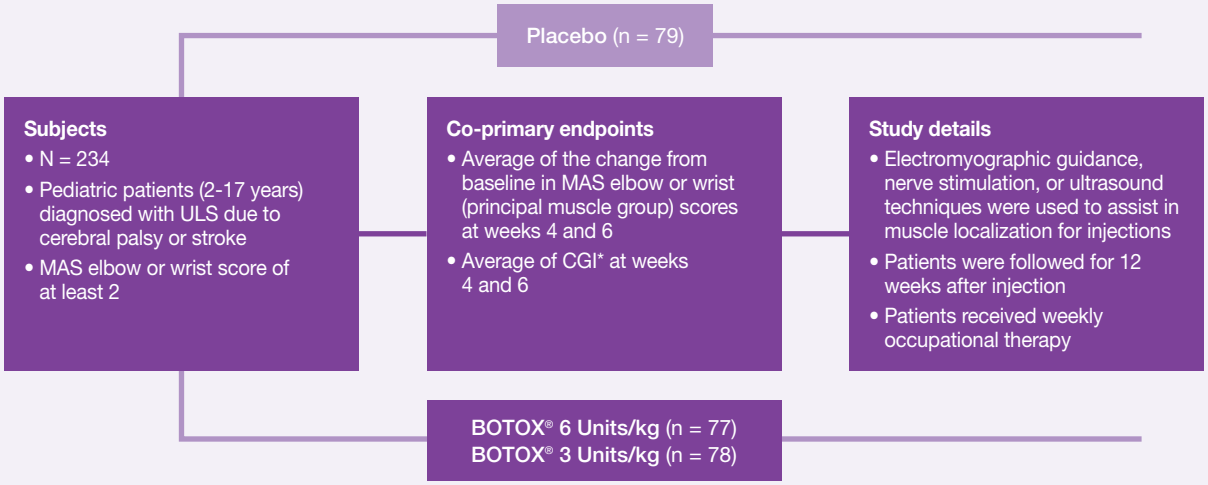
Hypersensitivity Reactions

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.

BOTOX® clinical efficacy

BOTOX® efficacy was demonstrated in Study 1 (NCT01603602): a randomized, multicenter, double-blind, placebo-controlled study (see Figure 28) (BOTOX® Prescribing Information).



*The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life, using a 9-point scale (-4 = very marked worsening to +4 = very marked improvement).

Figure 28. Study design of Pediatric Upper Limb Spasticity clinical trial (BOTOX® Prescribing Information; Data on file, AbbVie; Clinical Study Report 191622-101).

Patients received either BOTOX® 3 Units/kg (100 Units maximum), BOTOX® 6 Units/kg (200 Units maximum), or placebo injected intramuscularly and divided between the elbow or wrist and finger muscles (BOTOX® Prescribing Information).

Results of BOTOX® studied for Pediatric Upper Limb Spasticity

The co-primary endpoints were the average of the change from baseline in the MAS principal muscle group score (elbow or wrist) at weeks 4 and 6 and the average of the CGI at weeks 4 and 6.

Table 35. Co-primary Efficacy Endpoint Results (BOTOX® Prescribing Information)

	BOTOX® 3 Units/kg (n = 78)	BOTOX® 6 Units/kg (n = 77)	Placebo (n = 79)
Mean change from baseline in principal muscle group (elbow or wrist) on the modified Ashworth Scale Week 4 and 6 average	-1.92[a]	-1.87[a]	-1.21
Mean Clinical Global Impression score Week 4 and 6 average	1.88	1.87	1.66

[a] Nominal *P* value < 0.05.

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

Compared to placebo, significant improvements in the MAS change from baseline were observed at all time points for BOTOX® treated patients.

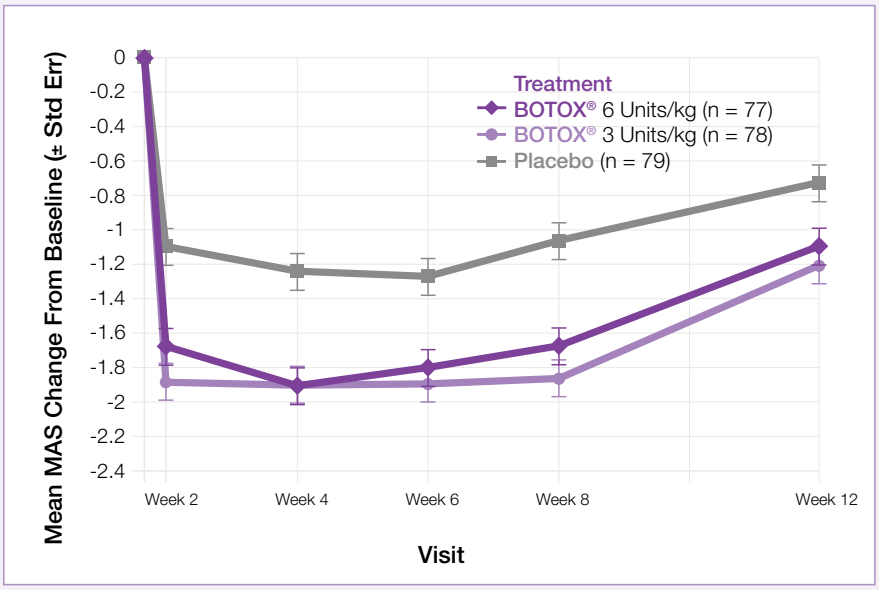


Figure 29. MAS elbow/wrist score (principal muscle group) over 12 weeks (BOTOX® Prescribing Information).

Although CGI scores numerically favored BOTOX® over placebo, the difference was not statistically significant.

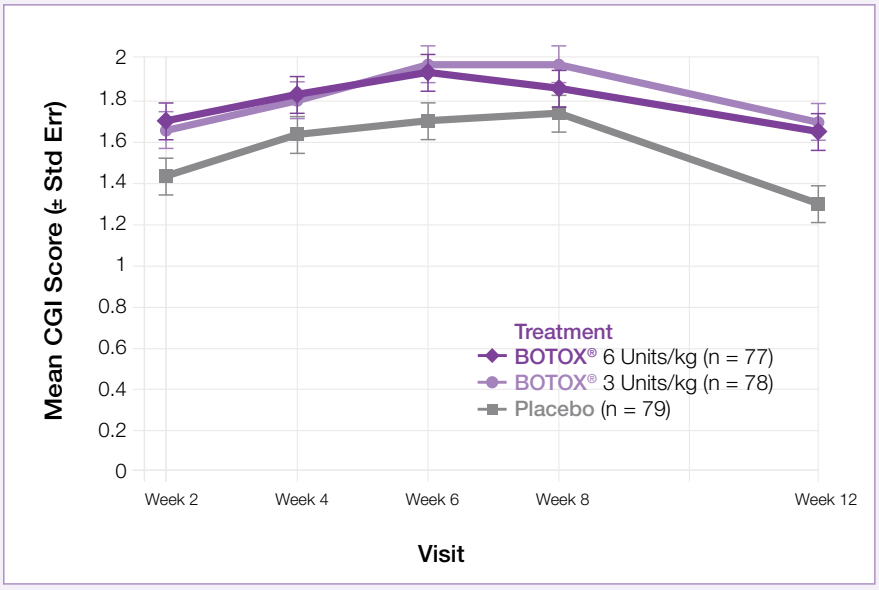


Figure 30. CGI score over 12 weeks (BOTOX® Prescribing Information).

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

BOTOX® adverse reactions in Pediatric Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® in pediatric patients 2 to 17 years of age with upper limb spasticity appear in Table 36. In a double-blind, placebo-controlled trial, 78 patients were treated with 3 Units/kg of BOTOX®, 77 patients received 6 Units/kg to a maximum dose of 200 Units of BOTOX®, and all were compared to 79 patients who received placebo.

Table 36. Adverse Reactions Reported by ≥ 2% of BOTOX® 6 Units/kg Treated Patients and More Frequent Than in Placebo-Treated Patients in a Pediatric Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (BOTOX® Prescribing Information)

Adverse Reactions	BOTOX® 6 Units/kg (n = 77) %	BOTOX® 3 Units/kg (n = 78) %	Placebo (n = 79) %
Infections and infestations			
Upper respiratory tract infection[a]	17	10	9
General disorders and administration site conditions			
Injection-site pain	4	3	1
Gastrointestinal disorders			
Nausea	4	0	0
Constipation	3	0	1
Respiratory, thoracic, and mediastinal disorders			
Rhinorrhea	4	0	1
Nasal congestion	3	0	1
Nervous system disorders			
Seizure[b]	5	1	0

[a] Includes upper respiratory tract infection and viral upper respiratory tract infection.

[b] Includes seizure and partial seizure.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Increased Risk of Clinically Significant Effects With Preexisting Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects, including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX (see *Warnings and Precautions*).

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

Pediatric Lower Limb Spasticity

Lower limb spasticity in pediatric patients may be due to a variety of neurologic conditions, including cerebral palsy, ischemic stroke, traumatic brain injury, and spinal cord injury. See Figure 25 for common clinical patterns that can help with assessment of Pediatric Lower Limb Spasticity.

BOTOX® treatment

Muscle selection and weight-based dosing

The recommended dose for treating Pediatric Lower Limb Spasticity is 4 Units/kg to 8 Units/kg divided among the affected muscles (see Table 37 and Figures 31 and 32) (BOTOX® Prescribing Information). The total dose of BOTOX® administered per treatment session in the lower limb should not exceed 8 Units/kg or 300 Units, whichever is lower. When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval.

Table 37. BOTOX® Dosing by Muscle for Pediatric Lower Limb Spasticity (BOTOX® Prescribing Information)

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

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 preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see *Boxed Warning*).

Pulmonary Effects of BOTOX in Patients With Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated With a Neurologic Condition

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

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

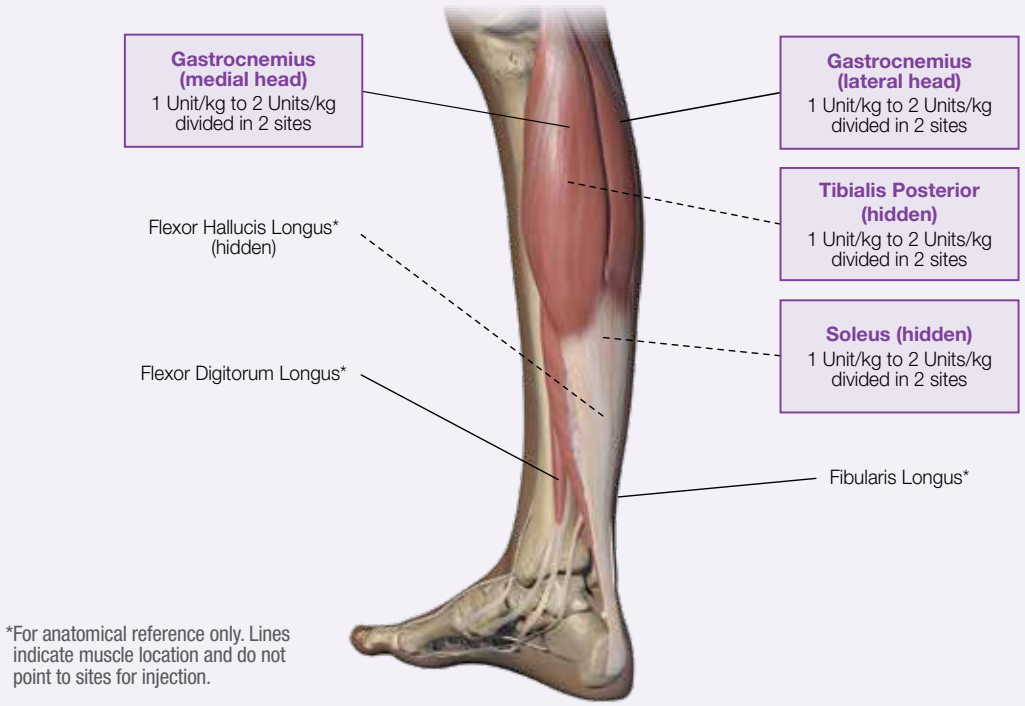


Figure 31. Muscles approved for BOTOX® injection in Pediatric Lower Limb Spasticity (BOTOX® Prescribing Information).

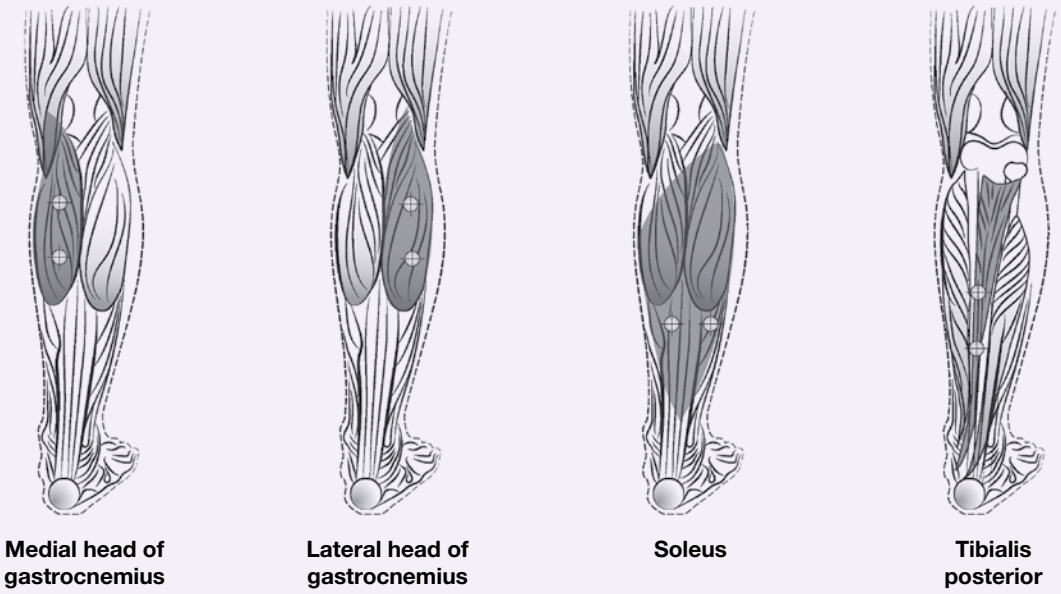
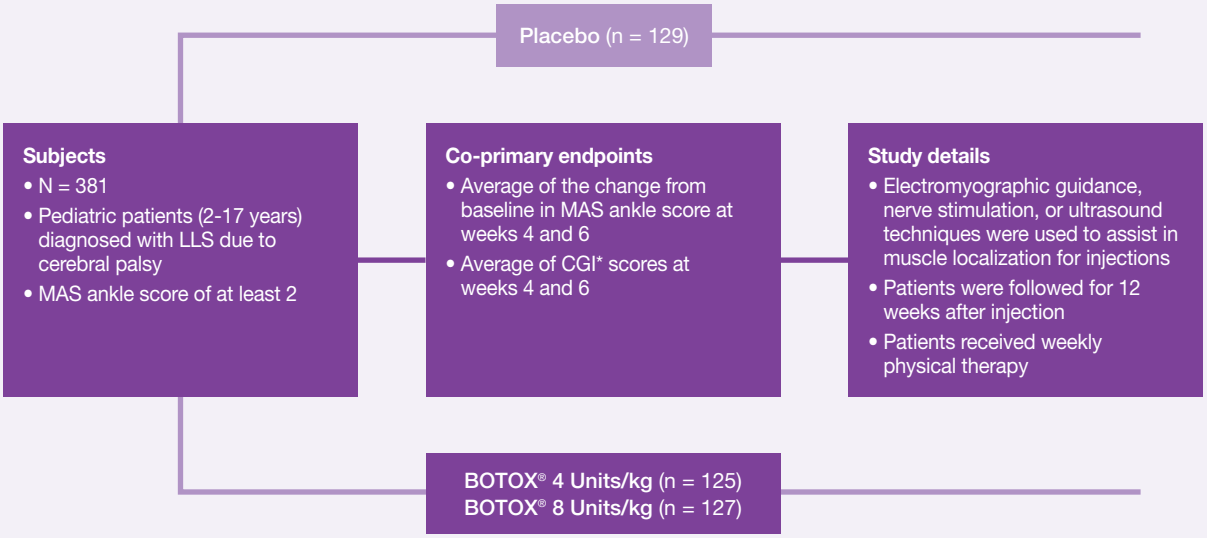


Figure 32. Injection sites for Pediatric Lower Limb Spasticity (BOTOX® Prescribing Information).

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

BOTOX® clinical efficacy

BOTOX® efficacy was demonstrated in Study 2 (NCT01603628): a randomized, multicenter, double-blind, placebo-controlled study (see Figure 33) (BOTOX® Prescribing Information).



*The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life, using a 9-point scale (-4 = very marked worsening to +4 = very marked improvement).

Figure 33. Study design of Pediatric Lower Limb Spasticity clinical trial (BOTOX® Prescribing Information; Data on file, AbbVie; Clinical Study Report 191622-111).

Patients received either BOTOX® 4 Units/kg (maximum 150 Units), BOTOX® 8 Units/kg (maximum 300 Units), or placebo injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior.

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

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.

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.

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

Results of BOTOX® studied for Pediatric Lower Limb Spasticity

The co-primary endpoints were the average of the change from baseline in the MAS ankle score at weeks 4 and 6, and the average of the CGI scores at weeks 4 and 6.

Statistically significant differences between BOTOX® and placebo were demonstrated for the MAS and CGI for the 8 Units/kg dose only (see Table 38).

Table 38. Co-primary Efficacy Endpoint Results (BOTOX® Prescribing Information)

	BOTOX® 4 Units/kg (n = 125)	BOTOX® 8 Units/kg (n = 127)	Placebo (n = 129)
Mean Change from Baseline in Plantar Flexors on the modified Ashworth Scale Week 4 and 6 average	-1.01[b]	-1.06[a]	-0.80
Mean Clinical Global Impression score Week 4 and 6 average	1.49	1.65[a]	1.36

[a]Significantly different from placebo ($P < 0.05$).
[b]Nominal P value < 0.05.

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 adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units to 360 Units total dose) compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

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

Compared to placebo, improvements in mean change from baseline for the MAS and mean CGI score for lower limb spasticity were observed at time points up to week 12 for BOTOX® treated patients (see Figure 34 and Figure 35).

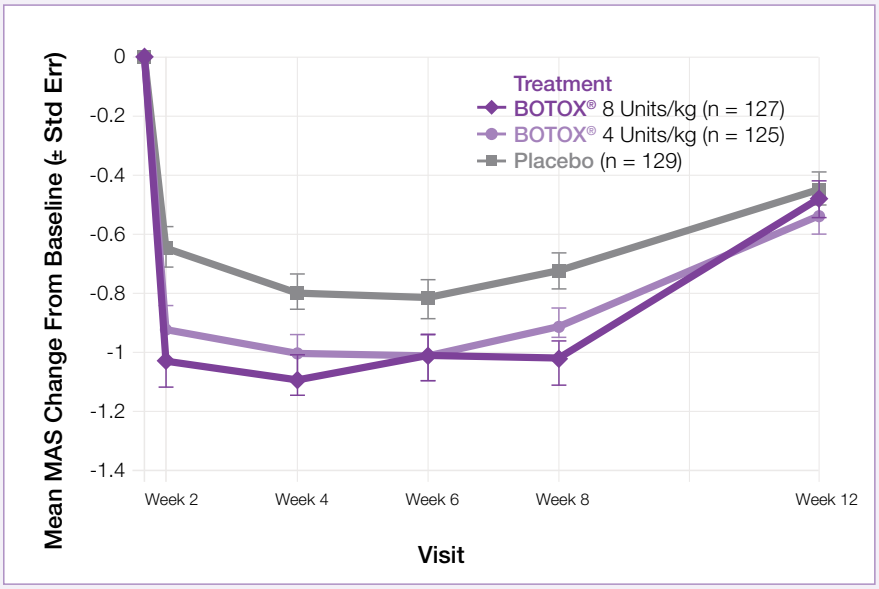


Figure 34. MAS ankle score over 12 weeks (BOTOX® Prescribing Information).

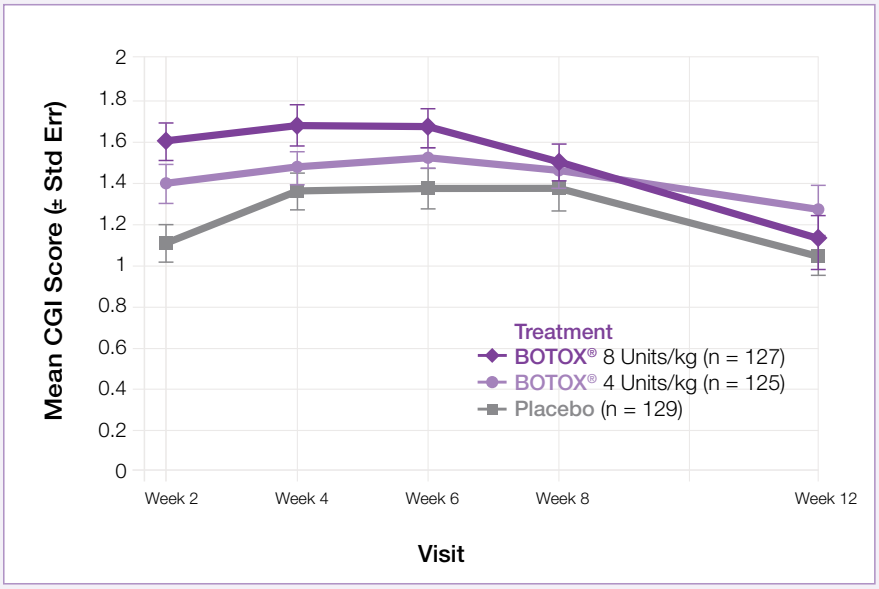


Figure 35. CGI score over 12 weeks (BOTOX® Prescribing Information).

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

BOTOX® adverse reactions in Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® in pediatric patients 2 to 17 years of age with lower limb spasticity appear in Table 39. In a double-blind, placebo-controlled trial (Study 2), 126 patients were treated with 4 Units/kg of BOTOX®, 128 patients received 8 Units/kg to a maximum dose of 300 Units of BOTOX®, and all were compared to 128 patients who received placebo.

Table 39. Adverse Reactions Reported by ≥ 2% of BOTOX® 8 Units/kg Treated Patients and More Frequent Than in Placebo-Treated Patients in a Pediatric Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (BOTOX® Prescribing Information).

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

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

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

Severe Primary Axillary Hyperhidrosis

BOTOX® Indication

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

Limitations of Use

The safety and effectiveness of BOTOX® for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.

Description

Axillary hyperhidrosis is a disorder in which axillary (underarm) sweat is secreted well in excess of the amount needed to meet the normal physiological requirements of the body (Atkins and Butler, 2002). Recommended criteria for diagnosis of primary focal hyperhidrosis include the presence of the condition for at least 6 months without apparent cause and at least 2 of the additional characteristics listed in Table 40 (Hornberger et al, 2004).

Etiology

The cause of severe primary axillary hyperhidrosis is unknown and has not been well studied. Sweat secretion is controlled by the body's thermoregulatory center, located in the hypothalamus. Hyperactivity or dysregulation of the autonomic nervous system has been postulated as the cause of severe primary hyperhidrosis (Haider and Solish, 2005). A genetic component to primary hyperhidrosis has also been suggested.

Table 40. Diagnostic Criteria for Severe Primary Focal Axillary Hyperhidrosis

Focal, visible, severe sweating of at least 6 months duration with frequency of at least 1 episode per week without apparent cause and at least 2 of the following characteristics:
• Bilateral and relatively symmetric
• Significant impairment in daily activity
• Frequency of at least 1 episode per week
• Age of onset less than 25 years
• Positive family history
• Cessation of focal sweating during sleep

From Hornberger et al, 2004.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Urinary Tract Infections in Patients With Overactive Bladder
BOTOX increases the incidence of UTI. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

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

Impact on patients

Although severe primary axillary hyperhidrosis does not affect a large group of individuals, it is an important disorder to recognize because of its potential effect on daily activities of those afflicted with the condition. In a randomized, controlled study of patients with primary axillary hyperhidrosis, approximately 75% of the 320 patients reported changing their clothing 2 or more times per day due to their hyperhidrosis (Naumann et al, 2002).

Measuring hyperhidrosis

As with any medical condition, measurement of hyperhidrosis is critical in determining disease severity and response to treatment. In clinical research studies, severe primary axillary hyperhidrosis has been measured using gravimetric assessment of sweat production over a given amount of time (Naumann and Lowe, 2001). The procedure usually involves placing a filter paper or other absorbent material over the hyperhidrotic area and securing it in place. After a specified amount of time, the paper is removed and weighed. The weight of the filter paper increases with increasing sweat secretion.

Gravimetric assessment allows quantification of sweat production. However, it may be too complex for routine clinical use (Campanati et al, 2003). Additionally, a given amount of sweating may be perceived as more of a problem by some individuals than others.

The Hyperhidrosis Disease Severity Scale (HDSS) is a patient-rated measure that evaluates the interference of axillary hyperhidrosis with daily activities (see Table 41). This scale was used as the primary endpoint measure in the pivotal trial leading to the FDA approval of BOTOX® for the treatment of severe primary axillary hyperhidrosis that is not adequately managed with topical agents (BOTOX® Prescribing Information; Lowe et al, 2007).

Providers of care

Dermatologists are expected to be the primary providers of care for individuals with severe primary axillary hyperhidrosis inadequately managed with topical agents who have elected to receive BOTOX® injections.

Current treatment options

Many patients who present to physicians with severe primary axillary hyperhidrosis have tried over-the-counter topical antiperspirants (Naumann et al, 2002). The next step for most patients is topical aluminum chloride (10%-35%) hexahydrate solution, as recommended by international treatment consensus guidelines (Hornberger et al, 2004). This antiperspirant is usually applied at night and washed off in the morning. Although topical aluminum chloride is effective for some patients, some may not obtain adequate benefit (Naumann et al, 2002).

Table 41. Hyperhidrosis Disease Severity Scale (HDSS)

A 4-point scale for categorizing the severity of primary axillary hyperhidrosis (BOTOX® Prescribing Information; Lowe et al, 2007).

My underarm sweating is:	
1	Never noticeable and never interferes with my daily activities
2	Tolerable but sometimes interferes with my daily activities
3	Barely tolerable and frequently interferes with my daily activities
4	Intolerable and always interferes with my daily activities

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

Urinary Retention in Adults Treated for Bladder Dysfunction

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

In patients who are not catheterizing, PVR urine volume should be assessed within 2 weeks posttreatment 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.

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

BOTOX® treatment

Botulinum Toxin Type A has long been known to block exocytosis of acetylcholine from sudomotor nerve terminals in experimental animals (Ambache, 1951). Since 2004, BOTOX® has been approved in the United States for the treatment of severe primary axillary hyperhidrosis that is inadequately controlled with topical agents (BOTOX® Prescribing Information).

Limitations of Use

The safety and effectiveness of BOTOX® for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.

BOTOX® is also approved in 79 additional countries for the treatment of severe primary axillary hyperhidrosis that is inadequately controlled with topical agents.

Dosing and administration

In the treatment of severe primary axillary hyperhidrosis inadequately managed with topical agents, the recommended starting dose of BOTOX® treatment is 50 Units per axilla injected intradermally into 10 to 15 sites (BOTOX® Prescribing Information). The hyperhidrotic area should be defined using a standard staining technique such as Minor's Iodine-Starch Test. For this test, patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for the previous 24 hours. Patients should rest comfortably without exercise, hot drinks, etc, for approximately 30 minutes prior to the test. The underarm area should then be dried and immediately painted with iodine solution. Once dry, the underarm should be lightly sprinkled with starch powder, and the excess blown away. The hyperhidrotic area will develop a deep blue-black color as the sweat permits chemical reaction between the iodine and the starch over approximately 10 minutes.

BOTOX® is reconstituted only with 0.9% nonpreserved sterile saline (100 Units/4 mL). The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Table 48 on page 90). Using a 30-gauge needle, 50 Units of BOTOX® (2 mL) is injected intradermally in 0.1-mL to 0.2-mL aliquots to each axilla, evenly distributed in multiple sites (10-15) approximately 1 cm to 2 cm apart. Larger surface areas of sweat may require more injection sites.

Figure 36. BOTOX® injection technique for severe primary axillary hyperhidrosis.

Each injection site produces a ring of effectiveness of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced. Each dose is injected to a depth of approximately 2 mm and at a 45-degree angle to the skin surface, with the bevel side up to minimize leakage and to ensure that the injections remain intradermal. If a physician elects to diagram the injection sites on a patient using a pen or marker, care should be taken not to put the needle directly through the ink mark to avoid a permanent tattoo effect.

Repeat injections for hyperhidrosis should be administered when the clinical effect of the previous injection diminishes. In the pivotal studies, the median duration of response to BOTOX® in severe primary axillary hyperhidrosis was 201 days (6.7 months). Among patients who received a second BOTOX® injection, the median duration of response was similar to the first (BOTOX® Prescribing Information).

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

BOTOX® clinical efficacy

The clinical efficacy of BOTOX® in the treatment of primary axillary hyperhidrosis has been demonstrated in 2 large, randomized, multicentered, placebo-controlled, double-blind clinical trials (BOTOX® Prescribing Information). In 1 study, 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 in adult patients with persistent primary axillary hyperhidrosis who had HDSS scores of 3 or 4 and produced at least 50 mg of sweat in each axilla at rest over 5 minutes. This study used a strict statistical endpoint: at least a 2-point reduction in scores on the HDSS scale 4 weeks after each of 2 consecutive treatments or a sustained response after treatment 1 without a second treatment.

In this study, 55% of patients (57/104) treated with 50 Units and 49% of patients (54/110) treated with 75 Units achieved HDSS score change ≥ 2, compared with 6% of patients (6/108) treated with placebo ($P < 0.001$), but was not significantly different between the two BOTOX® doses. The recommended dose for BOTOX® is 50 Units per axilla (Lowe et al, 2007).

In another Phase 3 study, 320 patients with bilateral primary axillary hyperhidrosis were randomized to receive either 50 Units of BOTOX® therapy (n = 242) or placebo (n = 78) in a single treatment session (BOTOX® Prescribing Information). Treatment responders were defined as those who showed at least a 50% reduction from baseline in axillary sweating measured by gravimetry at 4 weeks. At week 4 post injection, the percentages of responders were 91% (219/242) in the BOTOX® group and 36% (28/78) in the placebo group ($P < 0.001$). The difference in percentage of responders between BOTOX® neurotoxin treatment and placebo was 55% (95% CI = 43.3, 65.9) (BOTOX® Prescribing Information).

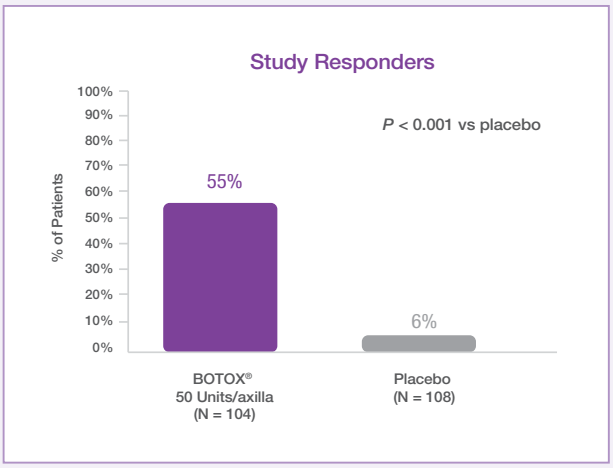


Figure 37. Patients achieving the primary endpoint with statistical significance in a Phase 3 study of 320 patients.

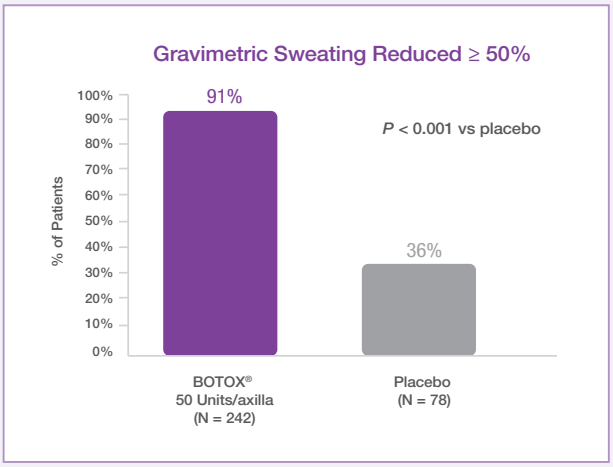


Figure 38. Patients achieving ≥ 50% reduction in gravimetric sweating in a Phase 3 study of 320 patients.

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

Severe primary axillary hyperhidrosis is typically a chronic condition and, as such, repeated injections of BOTOX® are likely to be needed. 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.

Adverse reactions profile

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

The data reflect 346 patients exposed to BOTOX® therapy (50 Units) and 110 patients exposed to BOTOX® therapy (75 Units) in each axilla.

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 (eg, hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Place of BOTOX® in the treatment algorithm

Evidence-based consensus guidelines have been developed for the treatment of axillary hyperhidrosis (Hornberger et al, 2004). These guidelines indicate that intradermal injections of Botulinum Toxin Type A may be administered to patients who have not attained adequate benefit from topical over-the-counter antiperspirants or aluminum chloride solutions (Hornberger et al, 2004).

Treatment Algorithm for Primary Focal Axillary Hyperhidrosis

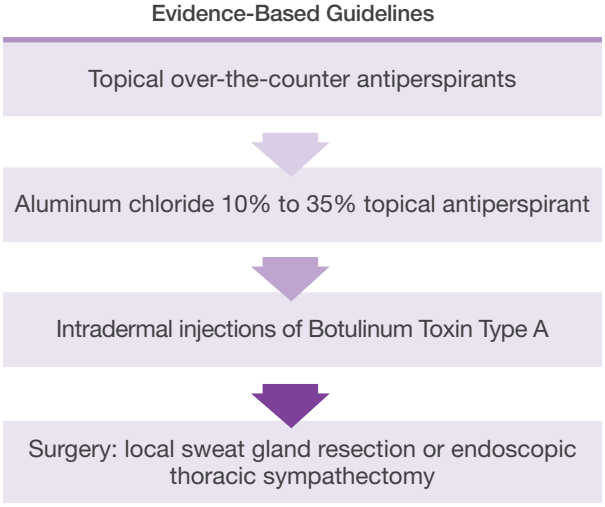


Figure 39. Evidence-based treatment algorithm as recommended by a group of international, multispecialty experts published in the *Journal of the American Academy of Dermatology* (Hornberger et al, 2004).

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Urinary Retention in Adults Treated for Bladder Dysfunction (continued)
Overactive Bladder
In clinical trials, 6.5% of patients (36/552) initiated CIC for urinary retention following treatment with BOTOX 100 Units, as compared to 0.4% of patients (2/542) treated with placebo. The median duration of catheterization for patients treated with BOTOX 100 Units was 63 days (minimum 1 day to maximum 214 days), as compared to a median duration of 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

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

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

Cervical Dystonia

BOTOX® Indication

BOTOX® for injection 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.

Description

Cervical Dystonia is a movement disorder characterized by patterned, repetitive, and spasmodic or sustained muscle contractions that result in abnormal movements and postures of the head and neck (Jankovic, 2004). Neck pain is a hallmark symptom of Cervical Dystonia, occurring in 75% of patients (Chan et al, 1991).

Head and neck deviations in Cervical Dystonia may occur in any direction (Figure 40). The head may tilt forward (anterocollis), backward (retrocollis), or laterally (laterocollis), or may twist toward the shoulder (torticollis). Most patients show a complex array of head deviations that are not confined to any single plane (Dauer et al, 1998). Although this disorder is sometimes referred to as *spasmodic torticollis*, *Cervical Dystonia* is the preferred term because contractions may or may not be spasmodic, and head rotation (torticollis) may or may not be present (Jankovic et al, 1991).

Torticollis 82% | Laterocollis 42% | Anterocollis 25% | Retrocollis 29%

Most patients show a combination of these postures (Jankovic et al,1991).

Figure 40. Various types of head postures in Cervical Dystonia (percentage of patients).

Table 42. Percentage of Cervical Dystonia Patients Showing Various Types of Head Postures

	Jankovic et al, 1991 (300 patients)
Torticollis	82%
Laterocollis	42%
Retrocollis	29%
Anterocollis	25%

Classification and etiology

Like other dystonias, Cervical Dystonia may be classified according to etiology, distribution of signs and symptoms, and age of onset (childhood/adolescence vs adulthood) (Fahn et al, 1987; Velickovic et al, 2001). The etiology of Cervical Dystonia may be primary (idiopathic) or secondary (symptomatic). Patients with idiopathic Cervical Dystonia have no evidence of any secondary cause of the dystonic symptoms, with the exception of primary dystonia genes (Velickovic et al, 2001). In symptomatic Cervical Dystonia, the abnormal neck postures and movements are due to some other underlying condition such as central or peripheral trauma, certain drugs, neurodegenerative disease, or other basal ganglia disorders (Velickovic et al, 2001). Approximately 9% to 11% of patients with Cervical Dystonia have a history of head or neck trauma preceding the onset of dystonia (Chan et al, 1991; Jankovic et al, 1991).

Epidemiology and clinical characteristics

Cervical Dystonia is the most common focal dystonia (Velickovic et al, 2001). It is estimated that in the United States, Cervical Dystonia affects 390 people in every 100,000 (Jankovic et al, 2007). Variable presentation, poor recognition, delayed diagnosis, and differences in methodologies may lead to underdiagnosis (Jankovic et al, 2007; Van Zandijcke, 1995).

Cervical Dystonia usually begins between the ages of 30 and 50 years, with neck stiffness and restricted head mobility reported as common initial symptoms (Tarsy and Simon, 2006). Because of these initial symptoms, Cervical Dystonia is often misdiagnosed as a musculoskeletal disorder (Tarsy and Simon, 2006). Like other focal dystonias, Cervical Dystonia is usually first seen by primary care physicians and other subspecialists rather than neurologists (Tarsy and Simon, 2006). Cervical Dystonia more commonly affects women than men (Chan et al, 1991; Jankovic et al, 1991). The condition can be primary (idiopathic) or secondary (symptomatic) (Fahn et al, 1987). Idiopathic Cervical Dystonia has been associated with genetic abnormalities (Placzek et al, 2001), although a causal role has not yet been established. Cervical Dystonia is progressive, and the change from mild to severe disease state may be gradual or sudden (Stacy, 2000). Clinical experience shows that symptoms tend to plateau within 5 years (Jankovic et al, 1991).

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
Urinary Retention in Adults Treated for Bladder Dysfunction (continued)
Adult Detrusor Overactivity Associated With a Neurologic Condition
In clinical trials, 30.6% of adult patients (33/108) who were not using CIC prior to injection required catheterization for urinary retention following treatment with BOTOX 200 Units, as compared to 6.7% of patients (7/104) treated with placebo. The median duration of postinjection catheterization for these patients treated with BOTOX 200 Units (n = 33) was 289 days (minimum 1 day to maximum 530 days), as compared to a median duration of 358 days (minimum 2 days to maximum 379 days) for patients receiving placebo (n = 7).

Among adult patients not using CIC at baseline, those with multiple sclerosis were more likely to require CIC postinjection than those with spinal cord injury.

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

A characteristic feature of Cervical Dystonia is the sensory trick, or *geste antagoniste*; by touching their faces, chins, or heads, individuals with Cervical Dystonia can often temporarily reduce dystonic symptoms. This feature is useful in the diagnosis of Cervical Dystonia. Many patients develop a habit of using such sensory tricks to improve posture. Sensory tricks tend to be more effective in the early stages of the disorder (Dauer et al, 1998).

Table 43. Cervical Dystonia Epidemiology

Demographics	
Average age of onset	≈ 41 years
Male:female ratio	1:1.5 to 1:1.9
Prevalence	
US study (2007)	390/100,000

Chan et al, 1991; Jankovic et al, 1991; Jankovic et al, 2007.

Symptoms

The most common presenting symptom in patients with Cervical Dystonia is a pulling sensation in the neck, followed by tremor, pain, jerking, and stiffness or tightness (Jankovic et al, 1991). Tremor is a common feature of Cervical Dystonia, occurring in approximately 70% of patients, of which 60% exhibit tremor of the head/neck and 32% exhibit tremor in other body regions (Jankovic et al, 1991). Shoulder elevation is observed in more than half of Cervical Dystonia patients, and 39% have scoliosis (Jankovic et al, 1991).

The course of Cervical Dystonia is variable within an individual over time and among different individuals, but it is typically a chronic condition. Although approximately 20% of patients experience spontaneous remission at some point, remissions are often transient (Jahanshahi et al, 1990).

Neck pain is a distinguishing feature of Cervical Dystonia (Chan et al, 1991), with 75% of 266 patients reporting neck pain. The pain is rated as moderate or severe in nearly 70% of patients (Chan et al, 1991). Neck pain in Cervical Dystonia is a major source of disability and is associated with tonic contractions, significantly greater severity of head turning, and the presence of spasms (Chan et al, 1991).

Diagnosis

Cervical Dystonia can be difficult to diagnose, and individuals may go undiagnosed for 1 year or more (Van Zandijcke, 1995). In the interim, many patients visit multiple healthcare practitioners for their symptoms, which can vary widely in presence and severity (Jankovic et al, 1991; van Herwaarden et al, 1994; Van Zandijcke, 1995).

Head position may deviate along a single plane or multiple planes, and combinations of different head positions are frequently noted (Jankovic et al, 1991).

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.

In idiopathic Cervical Dystonia, blood tests and magnetic resonance imaging (MRI) findings may be used to rule out underlying conditions (National Organization for Rare Disorders, 2015) and neurological examination is otherwise usually normal (Stacy, 2000). Several questions on the Beth Israel Dystonia Screen (BIDS) (Saunders-Pullman et al, 2005) have been proposed as useful in the screening for Cervical Dystonia, as shown in the table below (Table 44).

Vigilance and recognition of subtle Cervical Dystonia symptoms may facilitate evaluation and earlier diagnosis of the disorder.

Table 44. Screening Questions for Cervical Dystonia (Saunders-Pullman et al, 2005)

- Do your shoulders lift or pull up or down without your control?
- Have other people told you that your head pulls to either side, forward, or backward?
- Have other people told you that you have a head tremor?
- Do you have pain or stiffness in your neck most of the time?
- Is there a position you can put your head in to make the movement or pain stop?
- Did you ever see a doctor about head turning or shaking?

Table 45. Screening Tips and Tools for Evaluating Cervical Dystonia

History
- Listen to patient's description of symptoms
- Evaluate any reported pain
- Ask about previous neck trauma

Exam
- Observe patient's gait
- Use distracting maneuvers to get head to neutral point
- Ask patient to write, and observe posture
- Ask patient to close eyes, and observe posture
- Look for patient's use of sensory tricks or *gestes antagonistes*
- Examine entire body for subtle signs of dystonia, such as abnormal head positioning
- Examine patient from different angles
- Look for sagittal displacement of neck
- Evaluate patient's ability to turn head to each side

Tests
- Use MRI to rule out possible causes of symptoms
- Use EMG to confirm abnormal muscle activity
- Quantify overall disease burden with Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) (Consky and Lang, 1994), including:
  - Severity scale
  - Pain scale

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

BOTOX® treatment

A first-line treatment for Cervical Dystonia

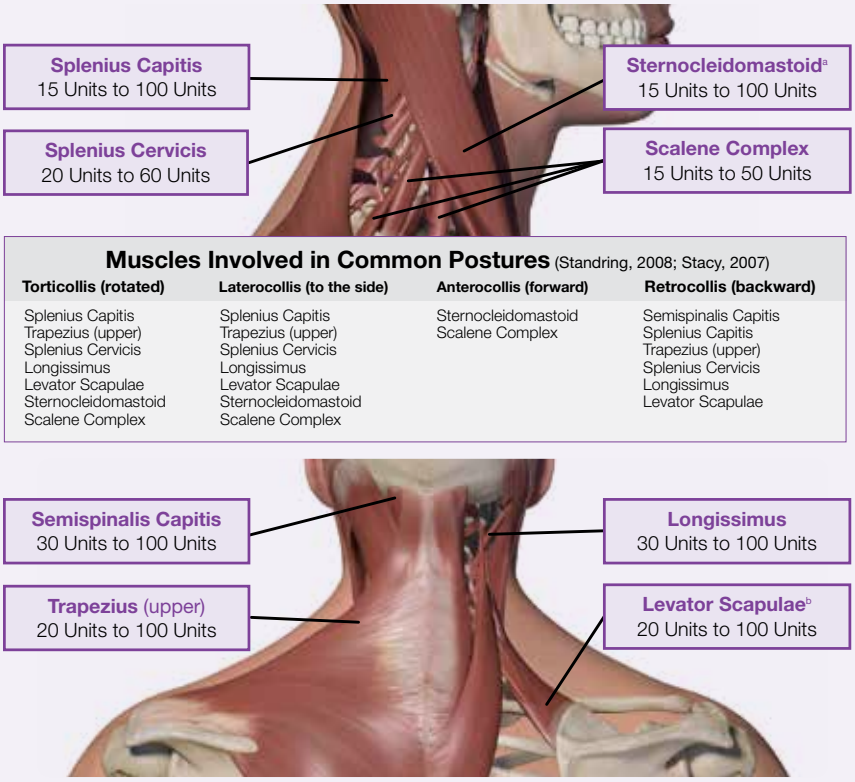
BOTOX® offers effective and locally administered treatment that makes it a first-line therapy for treating adult patients with mild, moderate, and severe Cervical Dystonia (BOTOX® Prescribing Information).

BOTOX® neurotoxin is administered through local injection into appropriate neck and/or shoulder muscles, where it acts to reduce contractions. Injections can be precisely placed into selected hyperactive muscles. Reduced muscle activity can be achieved by regulating the dose injected into specific muscles.

Muscle selection

Successful BOTOX® treatment in Cervical Dystonia is based on a thorough knowledge of the muscles controlling head and neck movement (Dubinsky, 1994). Key muscles involved in head position include the sternocleidomastoid, splenius capitis and cervicis, trapezius, levator scapulae, semispinalis capitis, scalene complex, and longissimus (Figure 41).

Muscle selection for injection may be based on the patient's head and neck position, localization of pain, and muscle hypertrophy (Poewe and Wissel, 1994). Spasm of the superficial neck muscles is generally detectable by palpating the affected area, but electromyographic (EMG) techniques are also commonly used. It should be noted that the pattern of muscle contraction may change over time (Gelb et al, 1991).



Muscles Involved in Common Postures (Standring, 2008; Stacy, 2007)

Torticollis (rotated)	Laterocollis (to the side)	Anterocollis (forward)	Retrocollis (backward)
Splenius Capitis	Splenius Capitis	Sternocleidomastoid	Semispinalis Capitis
Trapezius (upper)	Trapezius (upper)	Scalene Complex	Splenius Capitis
Splenius Cervicis	Splenius Cervicis		Trapezius (upper)
Longissimus	Longissimus		Splenius Cervicis
Levator Scapulae	Levator Scapulae		Longissimus
Sternocleidomastoid	Sternocleidomastoid		Levator Scapulae
Scalene Complex	Scalene Complex		

[a] If contributing, dose should be cut in half when injecting sternocleidomastoids for anterocollis. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk of dysphagia. Limiting the dose injected into the sternocleidomastoid muscle to ≤ 100 Units may decrease the occurrence of dysphagia. The initial dosing for a patient without prior use of BOTOX® should be at a lower dose, with subsequent dosing adjusted based on individual response.

[b] Usually injected if shoulder is involved. Injections to the levator scapulae may be associated with increased risk of upper respiratory infection and dysphagia.

Doses from Charles and Gill, 2010; and BOTOX® Prescribing Information.

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

Figure 41. Neck and shoulder muscles affected in Cervical Dystonia.

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

BOTOX® dosing

BOTOX® dosing should be tailored to each individual patient based on his or her head and neck positions, localization of pain, muscle hypertrophy, response, and adverse reaction history. The median total BOTOX® dose administered to patients in this study was 236 Units, with the 2 middle quartiles of patients receiving doses from 198 Units to 300 Units. It should be noted that these doses refer exclusively to BOTOX® and cannot be generalized to other botulinum neurotoxin preparations (BOTOX® Prescribing Information).

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with 0.9% nonpreserved sterile saline, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 48 on page 90).

In general, no more than 50 Units per site should 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 may be useful. Clinical improvement generally begins within the first 2 weeks after injection, with maximum clinical benefit at approximately 6 weeks post injection. In the Phase 3 study, most subjects were observed to have returned to pretreatment status by 3 months post treatment (BOTOX® Prescribing Information).

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS

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

Overactive Bladder

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

A higher incidence of UTI was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than nondiabetics.

The incidence of UTI increased in patients who experienced a maximum PVR urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% vs 23%, respectively.

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

BOTOX® clinical efficacy

The most important goals in treating Cervical Dystonia are to improve head position and to reduce pain (Charles et al, 2012). The effects of BOTOX® neurotoxin on these variables were assessed in a pivotal multicenter, double-blind trial in which 88 patients were treated with BOTOX® product (median total dose = 236 Units) and 82 patients were treated with placebo (Charles et al, 2012). Results of this study showed that BOTOX® provided significant benefit. BOTOX® significantly improved functioning and head position, and decreased the frequency and intensity of neck pain (Charles et al, 2012).

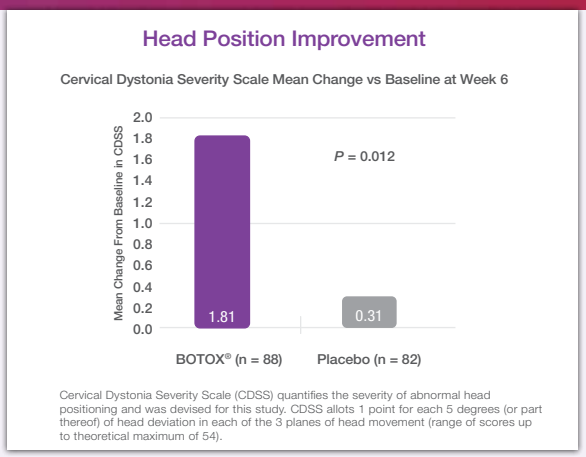


Figure 42. Head position improvement scores.

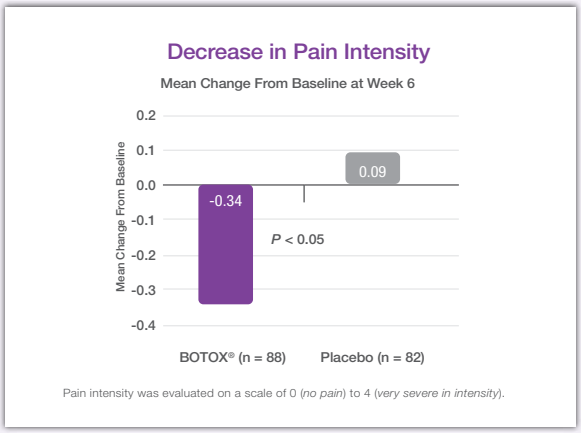


Figure 43. Decrease in pain intensity.

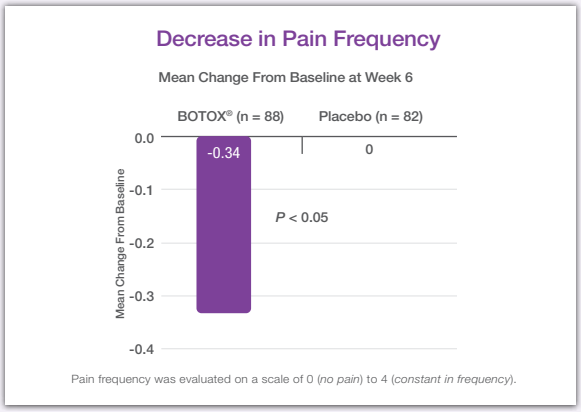


Figure 44. Decrease in pain frequency.

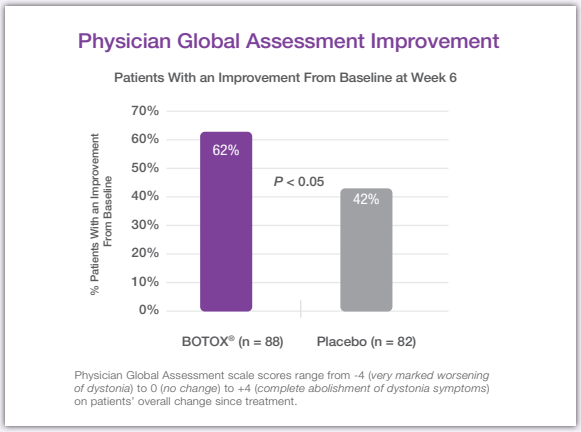


Figure 45. Physician Global Assessment improvement scores.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Adult Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions within 12 weeks of BOTOX injection for detrusor overactivity associated with a neurologic condition include UTI (BOTOX 24%, placebo 17%); urinary retention (BOTOX 17%, placebo 3%); and hematuria (BOTOX 4%, placebo 3%).

The following adverse event rates were reported at any time following initial injection and prior to reinjection or study exit (median duration of 44 weeks of exposure): UTIs (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

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

Treatment response

BOTOX® demonstrates a significant benefit in Cervical Dystonia patients. However, Cervical Dystonia is typically a chronic condition, and repeated injections are likely to be needed. The Prescribing Information for BOTOX® states that in the pivotal trial, the majority of patients with Cervical Dystonia returned to baseline within 3 months.

Most Cervical Dystonia patients continue to respond to repeated BOTOX® injections for many years (Hsiung et al, 2002), but some patients who were formerly responsive may cease to benefit from a subsequent treatment. In these cases, experts recommend a complete reassessment of the muscles involved, as changes in the pattern of muscle contractions may occur following treatment (Gelb et al, 1991) or due to the disease process itself (Münchau et al, 2001). In such cases, the appropriate doses and muscles injected may need to be altered.

Additionally, perceived improvements in head position and associated pain following subsequent injections may be less dramatic than those experienced after the initial injection (Brashear et al, 2000). This could be because symptoms have not returned to baseline levels between injections or because patients' perceptions have changed (Brashear et al, 2000).

Another factor that can affect treatment response is the formation of neutralizing antibodies. Although neither the presence nor the absence of neutralizing antibodies is a perfect predictor of clinical response, such antibodies may reduce the effectiveness of BOTOX® by inactivating the biological activity of the neurotoxin. The factors that contribute to neutralizing antibody formation have not been well studied. It is suggested that using the longest possible injection interval in order to minimize exposure to neurotoxin protein is an appropriate practice for minimizing the risk of neutralizing antibody formation (Greene et al, 1994).

Adverse reactions profile

The safety of BOTOX® for Cervical Dystonia patients has been evaluated in double-blind and open-label studies (BOTOX® Prescribing Information).

Table 46. The Most Frequently Reported Adverse Reactions With BOTOX® in Cervical Dystonia Trials

Adverse Reactions	BOTOX®
Dysphagia	19%
Upper respiratory tract infection	12%
Neck pain	11%
Headache	11%

Other reactions reported in 2% to 10% of patients in any one study, in decreasing order of incidence, include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea also have been reported. Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX® resulting from the spread of the toxin outside the injected muscles (BOTOX® Prescribing Information).

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

CASE STUDY: EK

Before BOTOX® treatment

After BOTOX® treatment

"About 2 weeks after my treatment I woke up on a Sunday morning and I sat on the side of the bed. And then I realized the pulling to the left had improved a bit."

Individual results may vary.

Figure 46. A Cervical Dystonia patient before and after BOTOX® treatment.

CASE STUDY: KH

Before BOTOX® treatment

After BOTOX® treatment

After 1 year of visits to multiple physicians and physical therapists, patient KH was finally diagnosed with Cervical Dystonia by a movement disorder specialist. She was immediately treated with BOTOX®.

"I was in constant pain, which affected my daily life."

Individual results may vary.

Figure 47. A Cervical Dystonia patient before and after BOTOX® treatment.

CASE STUDY: KK

Before BOTOX® treatment

After BOTOX® treatment

"My doctor said he was going to inject me with BOTOX® and that it would help with my head positioning and with the chronic neck pulling and aching, which makes me so stiff and in pain."

Patient profile

- Female
- Age: 32

Symptoms informing diagnosis

- Neck pain
- Stiffness
- Limited range of motion

Treatments preceding Cervical Dystonia diagnosis

- Integrative medicine (acupuncture, chiropractic adjustment)
- Traction
- Oral agents

Time since Cervical Dystonia diagnosis

- 2 years

Treatment regimen

- BOTOX® injections

Individual results may vary.

Figure 48. A Cervical Dystonia patient before and after BOTOX® treatment.

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

Blepharospasm

BOTOX® Indication

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

Description

Blepharospasm literally means *spasm of the eyelid*. It is characterized by involuntary, repetitive eyelid closure caused by contractions of the orbicularis oculi muscles. In the early stages, Blepharospasm may affect only 1 eye. However, both eyes eventually become involved (Jordan and Anderson, 1988).

If muscular contractions are confined to the eyelids, the condition is referred to as *essential blepharospasm.*

Etiology

Blepharospasm may be either idiopathic (primary) or secondary to another cause. It is important to distinguish between the 2 because recommended treatments differ. The cause of idiopathic blepharospasm is, by definition, unknown. The involvement of various brain regions, including the basal ganglia and brain stem, has been hypothesized; however, consistent neuropathological evidence is lacking (Jordan and Anderson, 1988). A genetic predisposition for Blepharospasm is suggested by the finding that 27% of patients have at least 1 first-degree relative affected by Blepharospasm or other adult-onset dystonia (Defazio et al, 2006).

The physical symptom of Blepharospasm or eyelid closure may be secondary to a variety of other conditions, including Parkinson's disease, Huntington's disease, and the use of certain drugs.

Patient characteristics

Blepharospasm affects nearly twice as many women as men, and the age of onset is typically 50 years or older (ESDE, 2000). The disorder is often preceded by other ocular symptoms such as photophobia or dry eye (Grandas et al, 1988). As the disorder progresses, patients experience sustained periods of eyelid closure that can significantly interfere with everyday activities. Eyelid spasms eventually develop, and many patients are rendered functionally blind.

Stress, fatigue, and bright lights may exacerbate Blepharospasm. Patients report temporary relief from symptoms while yawning, talking, humming, completing puzzles, playing the piano, and sleeping (Jordan and Anderson, 1988).

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions during the 12 weeks following BOTOX injection of 200 Units for pediatric detrusor overactivity associated with a neurologic condition include bacteriuria (20%), UTI (7%), leukocyturia (7%), and hematuria (3%).

The most common adverse reactions in patients who received BOTOX 6 Units/kg and less than a total dose of 200 Units were UTI, bacteriuria, and hematuria.

These patients were not adequately managed with at least one anticholinergic agent and were using CIC at baseline.

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

BOTOX® treatment

Thousands of patients have received BOTOX® for the treatment of Blepharospasm. When injected directly into hyperactive orbicularis oculi muscles, BOTOX® reduces the excessive contractions associated with this disorder. Since 1989, Botulinum Toxin Type A has been approved as a treatment for Blepharospasm (BOTOX® Prescribing Information).

CASE STUDY: AC

Before BOTOX® treatment

After BOTOX® treatment

"I experienced years of frustration trying to get an accurate diagnosis, because not many doctors had heard of this. I became, effectively, blind to the point that I couldn't even push my eyelids open with my fingers—they were so sore. I thought I was really on my way out of this world. It was very difficult for me and my family."

After BOTOX® treatment

"The BOTOX® *eventually kicked in, and I was so excited. I could keep my eyes open."*

Anita Croce
North-Central District Director
Benign Essential Blepharospasm
Research Foundation

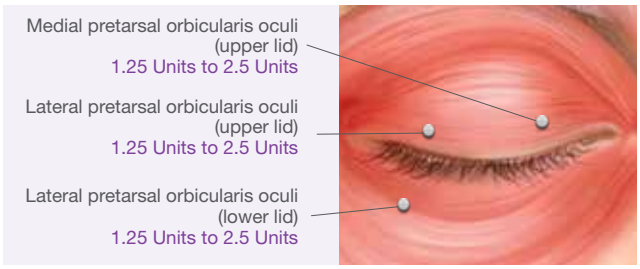
Individual results may vary.

Figure 49. A Blepharospasm patient before and after BOTOX® treatment.

Muscle selection and injection

BOTOX® should be reconstituted in sterile, preservative-free saline only and injected using a sterile, 27- to 30-gauge needle without EMG guidance. For Blepharospasm, the initial recommended dose is 1.25 Units to 2.5 Units (0.05-mL to 0.1-mL volume at each site) injected into the medial and lateral pretarsal orbicularis oculi of the upper lid and into the lateral pretarsal orbicularis oculi of the lower lid (Figure 50).

Figure 50. Eye muscles involved in Blepharospasm.



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 48 on page 90). The cumulative dose of BOTOX® treatment for Blepharospasm in a 30-day period should not exceed 200 Units.

In general, the initial effect of the injections is seen within 3 days and reaches a peak at 1 to 2 weeks post treatment. Each treatment lasts approximately 3 months, following which the procedure can be repeated.

Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues; this can be prevented by applying pressure at the injection site.

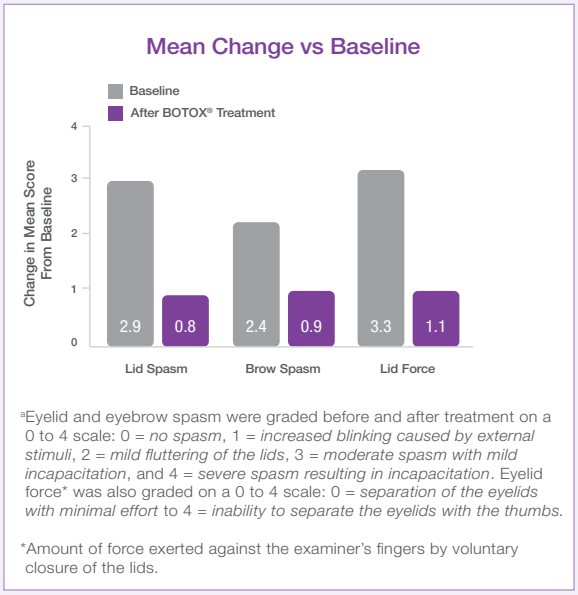
Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

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

BOTOX® clinical efficacy

The clinical efficacy of BOTOX® for the treatment of Blepharospasm has been examined in several studies.

In an open-label, historically controlled study, 27 patients with essential Blepharospasm were injected with BOTOX® (Arthurs et al, 1987; BOTOX® Prescribing Information). Improvement within 48 hours post injection was seen in 93% of patients, with effect reaching a peak at 1 to 2 weeks post treatment.



[a]Eyelid and eyebrow spasm were graded before and after treatment on a 0 to 4 scale: 0 = *no spasm*, 1 = *increased blinking caused by external stimuli*, 2 = *mild fluttering of the lids*, 3 = *moderate spasm with mild incapacitation*, and 4 = *severe spasm resulting in incapacitation*. Eyelid force* was also graded on a 0 to 4 scale: 0 = *separation of the eyelids with minimal effort* to 4 = *inability to separate the eyelids with the thumbs.*

*Amount of force exerted against the examiner's fingers by voluntary closure of the lids.

Figure 51. Mean scores for lid and brow spasm and lid force in patients with Blepharospasm before and after treatment with BOTOX® (n = 27).[a]

In a separate double-blind, placebo-controlled crossover trial, 12 patients with Blepharospasm received BOTOX® (n = 8) and/or placebo (n = 4). For patients treated with BOTOX®, mean dystonia scores improved by 72%, self-assessment ratings improved by 61%, and videotape evaluation rating scores improved by 39% (Jankovic and Orman, 1987). The effects of the treatment lasted for a mean duration of 12 weeks.

These data are supported by results from an open-label trial of 1684 patients with Blepharospasm (BOTOX® Prescribing Information). In this study, all patients showed clinical improvement, as evaluated by eyelid force and clinically observed intensity of lid spasm. On average, the beneficial effects of BOTOX® neurotoxin treatment lasted for 12 weeks prior to the need for re-injection.

Adverse reactions profile

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® product, the most frequently reported treatment-related adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other reactions 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 2 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.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Chronic Migraine

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

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

Strabismus

BOTOX® Indication

BOTOX® for injection is indicated for the treatment of Strabismus in patients 12 years of age and older.

Description

Strabismus is a group of disorders in which eye position deviates. In Strabismus, misalignment of the eyes results from the failure of eye muscles to work together. Strabismus is often classified based on the direction in which the eye deviates. The most common form is esotropia, or *convergent strabismus*, which occurs when the eye turns toward the nose. Exotropia, or *divergent strabismus,* occurs when the eye turns outward, away from the nose. One or both eyes may also turn up or down. Generally, the 2 eyes point in different directions. Strabismus may also be classified according to whether ocular deviation either varies (incomitant strabismus) or does not vary (comitant strabismus) with the direction of gaze. Ocular deviations in Strabismus are measured in terms of prism diopters (Cruz and Flynn, 1994).

Patient characteristics

The most obvious symptoms of Strabismus are misalignment of the eyes, uncoordinated eye movements, and double vision (Cruz and Flynn, 1994).

In diagnosing Strabismus, the patient is often asked to fixate on some object. One eye is then covered, and movement of the uncovered eye is assessed. In Strabismus patients, 1 eye is not aligned with the object of fixation. If the fixating eye is covered, the deviating eye will move rapidly to fixate. In contrast, the fixating eye will not move when the deviating eye is covered because it is already aligned with the object (Cruz and Flynn, 1994).

BOTOX® treatment

Figure 52. Eye turned inward in Strabismus.

The goal of BOTOX® treatment for Strabismus is to weaken the injected muscle long enough for it to become slightly atrophied or stretched. This allows the antagonist muscle to tighten or contract, which helps align the eyes. This process is thought to promote binocular motor fusion that stabilizes the alignment (Rowe and Noonan, 2012).

About one-half of Strabismus patients will require subsequent doses because of inadequate response. Subsequent injections may be necessary if the patient shows a large deviation or restriction, lack of binocular motor fusion, or inadequate muscle weakening in response to the initial injection (BOTOX® Prescribing Information).

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

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

Muscle selection and injection

For the treatment of Strabismus, the eye should be prepared for BOTOX® injection by giving several drops of a local anesthetic and an ocular decongestant a few minutes prior to injection. BOTOX® is intended for injection into extraocular muscles, utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique (BOTOX® Prescribing Information).

The volume of BOTOX® injected for treatment of Strabismus should be between 0.05 mL and 0.15 mL per muscle. The initial recommended doses of the reconstituted BOTOX® are shown in Table 47. The initial listed doses of the reconstituted BOTOX® (see Dosage and Administration section of BOTOX® Prescribing Information) typically create paralysis of the injected muscles beginning 1 to 2 days after injection and increasing in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a similar time period (BOTOX® Prescribing Information).

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

Table 47. BOTOX® Recommended Initial Doses for Strabismus

Muscle or Condition	Dose per Muscle
Vertical muscles	1.25 Units to 2.5 Units
Horizontal strabismus	
• < 20 prism diopters	1.25 Units to 2.5 Units
• 20 to 50 prism diopters	2.5 Units to 5 Units
Persistent VI nerve palsy ≥ 1 month	1.25 Units to 2.5 Units (in medial rectus muscle)
Maximum recommended dose for a single injection	25 Units

BOTOX® clinical efficacy

Strabismus was the first disorder to be treated with Botulinum Toxin Type A. In fact, the entire clinical development of botulinum neurotoxin therapy was the result of Dr. Alan B. Scott's search for an alternative to surgery for patients with Strabismus.

Since Dr. Scott's original reports, many published studies have examined Botulinum Toxin Type A as a treatment for Strabismus (Brin and Blitzer, 2013). In 1 open-label trial, 677 patients were treated with 1 or more injections of BOTOX® neurotoxin. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated 6 months or more following injection (BOTOX® Prescribing Information).

Adverse reactions profile

Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviation, especially with higher doses of BOTOX®. The incidence rates of these adverse reactions 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 (BOTOX® Prescribing Information).

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Adult 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.

BOTOX® format, injection guidelines, and reconstitution

BOTOX® neurotoxin is supplied in single-dose 100-Unit and 200-Unit quantities; each is packaged in a single-dose vial (Figure 53). The vial has a rounded interior to reduce waste. This design may permit easier extraction.

Figure 53. BOTOX® single-dose vials.

Unopened vials of BOTOX® should be stored in a refrigerator (2°C to 8°C) for up to 36 months. BOTOX® should not be used after the expiration date on the vial. BOTOX® neurotoxin should be administered within 24 hours of reconstitution in the vial. During this time period, unused reconstituted BOTOX® should be stored in a refrigerator (2°C to 8°C) for up to 24 hours until time of use. BOTOX® vials are for single-dose only. Discard any unused portion (BOTOX® Prescribing Information).

BOTOX® cartons have features to alert users if contents may have been compromised. Do not use BOTOX® and contact AbbVie (1-800-678-1605) if the tamper-evident features on the carton appear to be broken or compromised, or if the U.S. License number 1889 is not present on the vial label and carton labeling.

BOTOX® is supplied in crystalline form and should be reconstituted with preservative-free, normal, sterile saline (0.9% sodium chloride injection). A 1.5-inch or 2-inch, 21-gauge needle on a tuberculin-type syringe is used to draw up the desired amount of nonpreserved normal saline (see Table 48 below and Figure 55 on page 98) (BOTOX® Prescribing Information).

Table 48. BOTOX® Dilution Table

100-Unit BOTOX® Vial		
0.9% Sodium Chloride* per vial	Dose per 1-mL syringe	Dose per 0.1 mL
1 mL	100 Units	10 Units
2 mL	50 Units	5 Units
4 mL	25 Units	2.5 Units
8 mL	12.5 Units	1.25 Units
10 mL	10 Units	1 Unit
200-Unit BOTOX® Vial		
0.9% Sodium Chloride* per vial	Dose per 1-mL syringe	Dose per 0.1 mL
1 mL	200 Units	20 Units
2 mL	100 Units	10 Units
4 mL	50 Units	5 Units
8 mL	25 Units	2.5 Units
16 mL	12.5 Units	1.25 Units
20 mL	10 Units	1 Unit

*Preservative-free 0.9% Sodium Chloride Injection, USP only.

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

Important injection guidelines

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

Indication-specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for 1 or more indications, the maximum cumulative dose should not exceed 400 Units in a 3-month interval. In pediatric patients, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval (BOTOX® Prescribing Information).

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

BOTOX® is supplied in single-dose 100-Unit and 200-Unit vials. Prior to injection, reconstitute each vacuum-dried vial of BOTOX® with sterile, nonpreserved 0.9% sodium chloride injection USP. Draw up the proper amount of diluent in the appropriately sized sterile syringe, 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, unused reconstituted BOTOX® should be stored in a refrigerator (2°C to 8°C) for up to 24 hours until time of use. BOTOX® vials are for single-dose only. Discard any unused portion (BOTOX® Prescribing Information).

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Pediatric Upper Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX in pediatric upper limb spasticity include upper respiratory tract infection (includes upper respiratory tract infection and viral upper respiratory tract infection), injection-site pain, nausea, constipation, rhinorrhea, nasal congestion, and seizure (includes seizure and partial seizure).

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

Important injection guidelines (continued)

Adult Bladder Dysfunction:

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

Patients should discontinue antiplatelet therapy at least 3 days before the injection procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy (BOTOX® Prescribing Information).

Overactive Bladder

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

The recommended dose is 100 Units of BOTOX®, and is the maximum recommended dose. Reconstitute a 100-Unit vial of BOTOX® in 10 mL with 0.9% nonpreserved saline solution. Dispose of any unused saline (BOTOX® Prescribing Information).

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

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 55). 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 169 days [≈ 24 weeks]), but no sooner than 12 weeks from the prior bladder injection (BOTOX® Prescribing Information).

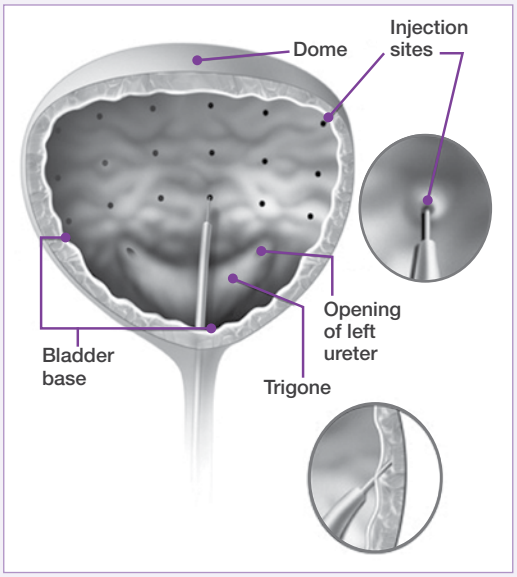


Figure 54. Injection pattern for intradetrusor injections for treatment of overactive bladder in adults and detrusor overactivity associated with a neurologic condition in adult and pediatric patients.

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

Adult Bladder Dysfunction (continued): Adult Detrusor Overactivity Associated With a Neurologic Condition

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

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

Reconstitute a 200-Unit vial of BOTOX® product with 6 mL of 0.9% nonpreserved saline solution and mix the vial gently. Draw 2 mL from the vial into each of three 10-mL syringes. Complete the reconstitution by adding 8 mL of 0.9% nonpreserved saline solution 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 (BOTOX® Prescribing Information).

Alternatively, reconstitute two 100-Unit vials of BOTOX®, each with 6 mL of 0.9% nonpreserved saline solution, 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 0.9% nonpreserved saline solution into each of the 10-mL syringes, and mix gently. This will result in three 10-mL syringes, each containing 10 mL (≈ 67 Units), for a total of 200 Units of reconstituted BOTOX® product. Use immediately after reconstitution in the syringe. Dispose of any unused saline (BOTOX® Prescribing Information).

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 overdistension should be avoided.

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

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

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

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Pediatric Lower Limb Spasticity
The most frequently reported adverse reactions following injection of BOTOX in pediatric lower limb spasticity include injection-site erythema, injection-site pain, oropharyngeal pain, ligament sprain, skin abrasion, and decreased appetite.

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

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

Patients must not have a urinary tract infection (UTI) at the time of treatment. Oral prophylactic antibiotics, except aminoglycosides, should be administered 1 to 3 days pre-treatment, on the treatment day, and 1 to 3 days post-treatment to reduce the likelihood of procedure-related UTI. Alternatively, for patients receiving general anesthesia (or conscious sedation) for the treatment of detrusor overactivity associated with a neurologic condition, one dose of IV prophylactic antibiotics, except aminoglycosides, may be administered prior to treatment administration on the day of treatment.

Patients should discontinue antiplatelet therapy at least 3 days before the injection procedure. Patients on anticoagulant therapy need to be managed appropriately to decrease the risk of bleeding (BOTOX® Prescribing Information).

Appropriate caution should be exercised when performing a cystoscopy.

- In patients 5 years to less than 12 years of age: Consider general anesthesia (or conscious sedation) prior to injection, per local site practice
- In patients 12 years of age or older: Consider an intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia prior to injection, per local site practice

At a minimum, consider a diluted instillation of local anesthetic for all age groups. If a local anesthetic instillation is performed, drain and irrigate the bladder with sterile saline before injection (BOTOX® Prescribing Information).

If the patient's body weight is greater than or equal to 34 kg, the recommended dosage is 200 Units of BOTOX® per treatment administered as an intradetrusor injection after dilution (BOTOX® Prescribing Information):

- Reconstitute BOTOX® to result in 20 Units BOTOX®/mL in the vial(s):
  - BOTOX® 200-Unit vial: Add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently
  - BOTOX® 100-Unit vials: Add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to each of two 100-Unit vials of BOTOX® and mix the vials gently
- Draw 10 mL from the vial(s) into one 10-mL dosing syringe
- Use immediately after reconstitution in the syringe. Dispose of any unused saline

If the patient's body weight is less than 34 kg, the recommended dosage is 6 Units/kg body weight administered as a bladder injection after dilution (refer to Table 48) (BOTOX® Prescribing Information):

- Reconstitute BOTOX® to result in 20 Units BOTOX®/mL in the vial(s):
  - BOTOX® 200-Unit vial: Add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently
  - BOTOX® 100-Unit vial(s): Add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to one 100-Unit vial of BOTOX® (if final dose is less than or equal to 100 Units) or to each of two 100-Unit vials of BOTOX® (if final dose is greater than 100 Units) and mix the vial(s) gently
- Refer to Table 49 for dilution instructions (ie, the amount of reconstituted BOTOX® and additional diluent to draw into one 10-mL dosing syringe)
- Use BOTOX® immediately after reconstitution in the syringe. Dispose of any unused preservative-free 0.9% Sodium Chloride Injection, USP

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

Table 49. BOTOX® Dilution Instructions and Final Dosing for Patients with Body Weight < 34 kg (BOTOX® Prescribing Information)

Body Weight (kg)	Volume of Reconstituted BOTOX® and Diluent* (mL) to Draw into Dosing Syringe to Achieve a Final Volume of 10 mL		Final Dose of BOTOX® in Dosing Syringe
	BOTOX® (mL)	Diluent* (mL)	
12 to less than 14	3.6	6.4	72 Units
14 to less than 16	4.2	5.8	84 Units
16 to less than 18	4.8	5.2	96 Units
18 to less than 20	5.4	4.6	108 Units
20 to less than 22	6	4	120 Units
22 to less than 24	6.6	3.4	132 Units
24 to less than 26	7.2	2.8	144 Units
26 to less than 28	7.8	2.2	156 Units
28 to less than 30	8.4	1.6	168 Units
30 to less than 32	9	1	180 Units
32 to less than 34	9.6	0.4	192 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP only.

Reconstituted BOTOX® 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 (BOTOX® Prescribing Information).

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 55). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX® in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post injection (BOTOX® Prescribing Information).

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, parallel group clinical study was 207 days [30 weeks] for BOTOX® 200 Units), but no sooner than 12 weeks from the prior bladder injection (BOTOX® Prescribing Information).

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

Important injection guidelines (continued)

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 48 on page 90). The recommended dose for treating Chronic Migraine is 155 Units administered intramuscularly (IM) 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 diagram in Figure 14 on page 37. A 1-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 1 site (midline), all muscles should be injected bilaterally, with half the number of injection sites administered to the left side and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks (BOTOX® Prescribing Information).

Adult 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 0.9% nonpreserved sterile saline (see Table 46 on page 83). 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 (BOTOX® Prescribing Information).

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 (BOTOX® Prescribing Information).

Pediatric Spasticity

Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended. Additional *general* Adult Spasticity dosing information (provided above) is also applicable to Pediatric Spasticity. When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval.

Primary Axillary Hyperhidrosis

The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Table 48 on page 90). Using a 30-gauge needle, 50 Units of BOTOX® (2 mL) are injected intradermally in 0.1-mL to 0.2-mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1 cm to 2 cm apart.

Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes (BOTOX® Prescribing Information).

Cervical Dystonia

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with 0.9% nonpreserved sterile saline, depending on volume and number of injection sites desired to achieve treatment objectives. In general, no more than 50 Units per site should 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 may be useful (BOTOX® Prescribing Information).

Clinical improvement generally begins within the first 2 weeks after injection, with maximum clinical benefit at approximately 6 weeks post injection. In the double-blind, placebo-controlled study, most subjects were observed to have returned to pretreatment status by 3 months post treatment (BOTOX® Prescribing Information).

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

Blepharospasm

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

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units, it is 100 Units/4 mL.

In general, the initial effect of the injections is seen within 3 days and reaches a peak at 1 to 2 weeks post treatment. Each treatment lasts approximately 3 months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to twofold if the response from the initial treatment is considered insufficient, usually defined as an effect that does not last longer than 2 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 3 months, and it is rare to have the effect be permanent (BOTOX® Prescribing Information).

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

Strabismus

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

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 (BOTOX® Prescribing Information).

The volume of BOTOX® injected for treatment of Strabismus should be between 0.05 mL and 0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX® (see Dosage and Administration section of BOTOX® Prescribing Information) typically create paralysis of the injected muscles beginning 1 to 2 days after injection and increasing in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a similar time period. Overcorrections lasting more than 6 months have been rare. About one-half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment (BOTOX® Prescribing Information).

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Cervical Dystonia

The most frequently reported adverse reactions following injection of BOTOX for cervical dystonia include dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

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

Preparation and dilution technique

Each single-dose vial contains 100 Units or 200 Units of vacuum-dried *Clostridium botulinum* Type A neurotoxin complex. Prior to intramuscular injection, reconstitute vacuum-dried BOTOX® product only with sterile, nonpreserved normal saline (0.9% sodium chloride injection) (BOTOX® Prescribing Information).

Using the reconstitution needle, draw up the proper amount of saline (see Table 48 on page 90) in the appropriately sized sterile syringe. A 21-gauge, 1.5-inch or 2-inch needle is recommended for reconstitution. Reconstituted BOTOX® should be clear, colorless, and free of particulate matter.

Insert the needle straight into the vial, then tilt the vial at a 45° angle. Slowly inject the saline into the BOTOX® neurotoxin vial. Vacuum is present in the vial, which demonstrates that the sterility of the vial is intact. Do not use the vial if the vacuum does not pull the saline into the vial.

Release the vacuum by disconnecting the syringe from the needle and allowing air to flow into the vial. Gently mix BOTOX® with the saline by moving vial side to side or rotating the vial.

Draw the fluid into the injection syringe by placing the needle into the bottom corner of the vial for full extraction.

Disconnect the injection syringe from the vial and attach an appropriately sized needle for injection. A 25-, 27-, or 30-gauge needle may be used for superficial muscles, and a longer 22-gauge needle may be used for deeper musculature.

Figure 55. BOTOX® reconstitution process.

Please see pages 90 to 97 for additional important injection guidelines for BOTOX®.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)

Blepharospasm

The most frequently reported adverse reactions following injection of BOTOX for blepharospasm include ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

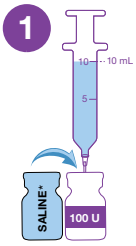
Please see additional Important Safety Information about BOTOX® on following pages.

Preparation and dilution technique for overactive bladder (OAB)

Reconstitution Procedure for OAB Using One 100-Unit BOTOX® Vial

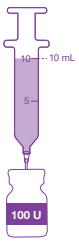
Prepare BOTOX® using aseptic technique.
Wipe the top of vials with an alcohol swab.

1



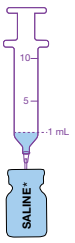
- Draw 10 mL of sterile, nonpreserved 0.9% saline into the syringe
- Inject saline into the 100-Unit BOTOX® vial. Mix gently by swirling the BOTOX® vial. Do not shake
- Administer within 24 hours after reconstitution in the vial. During this time, reconstituted BOTOX® should be stored in a refrigerator (2°C-8°C)

2



- Draw 10 mL of reconstituted BOTOX® from the 100-Unit BOTOX® vial into the 10-mL syringe
- Use BOTOX® immediately after reconstitution in the syringe. Do not store reconstituted BOTOX® in the syringe

3



- **In a separate syringe**, draw an additional 1 mL of saline for final flush

Result: One 10-mL syringe, for a total of 100 Units of reconstituted BOTOX® in 10 mL (dose of 5 Units per 0.5 mL) as well as a 1-mL syringe of saline for final flush.

*Unused saline should be discarded after each reconstitution procedure.

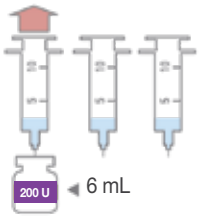
Reconstitution of one 100-Unit vial will result in 1 syringe. The total dose is 100 Units.

Preparation and dilution technique for Adult Detrusor Overactivity Associated with a Neurologic Condition

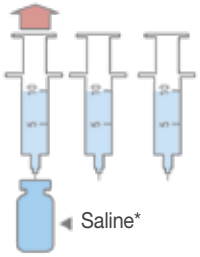
Using One 200-Unit BOTOX® Vial

1 Add 6 mL of 0.9% nonpreserved saline solution to the 200-Unit vial. **Mix gently.**

2 Draw 2 mL from the 200-Unit vial into each of three 10-mL syringes.



3 Add 8 mL of 0.9% nonpreserved saline solution into each of the 10-mL syringes. **Mix gently.**

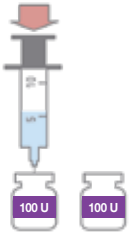


*Unused saline should be discarded after each reconstitution procedure.

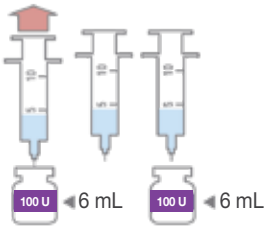
The various types of botulinum toxins have different dosing regimens and potency Units. The dosing Units are not interchangeable. This information is for BOTOX® only and cannot be applied to other botulinum toxins.

Using Two 100-Unit BOTOX® Vials

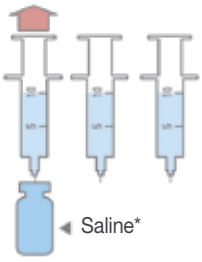
1 Add 6 mL of 0.9% nonpreserved saline solution to each 100-Unit vial. **Mix gently.**



2 Draw 4 mL from each 100-Unit vial into each of two 10-mL syringes. Then draw the remaining 2 mL from each 100-Unit vial into a third 10-mL syringe.



3 Add 6 mL of 0.9% nonpreserved saline solution into each of the 10-mL syringes. **Mix gently.**



*Unused saline should be discarded after each reconstitution procedure.

- Either procedure (reconstitution of one 200-Unit vial or two 100-Unit vials) will result in 3 syringes
- The total dose is 200 Units of BOTOX® at a concentration of ≈ 6.7 Units per mL
- Use immediately after reconstitution in the syringe. Dispose of any unused saline

Figure 56. BOTOX® reconstitution procedure for intradetrusor injection.

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

BOTOX® coding, reimbursement support, and patient assistance

BOTOX® coding

Table 50. BOTOX® Coding Information

BOTOX® Codes		
Code Type	**Code**	**Code Definition**
HCPCS II	J0585[a]	INJECTION, ONABOTULINUMTOXINA, 1 UNIT
NDC	00023-1145-01[b] 00023-3921-02[b]	BOTOX® 100-Unit vial BOTOX® 200-Unit vial

[a] The descriptor for J0585 requires that BOTOX® be billed by number of Units, not number of vials.

[b] For electronic billing, payers require an 11-digit NDC number (5-4-2 configuration) to be reported on the claim form. Therefore, an additional zero should be added to the beginning of the 10-digit NDC code listed on the box (eg, 00023-1145-01).

BOTOX® reimbursement support

Over 20 years of reimbursement experience

- AbbVie can provide assistance throughout the BOTOX® reimbursement and treatment process
- We can provide BOTOX® related considerations in the following areas:
  - Drug acquisition options
  - Obtaining insurance verification and prior authorization approvals
  - Patient scheduling
  - Documentation and patient tracking
  - Billing and coding

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Strabismus
The most frequently reported adverse events following injection of BOTOX for strabismus include ptosis (1% after inferior rectus injections, 16% after horizontal rectus injections, and 38% after superior rectus injections) and vertical deviation (17%).

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

Program to help with BOTOX® patient costs

BOTOX® Savings Program

The BOTOX® Savings Program can help eligible patients save on their out-of-pocket costs.

Patient eligibility criteria:

- Must have commercial health insurance or commercial prescription drug insurance
- Is not enrolled in either Medicare, Medicare Advantage, Medicaid, or a VA/DOD health plan
- Is not Medicare eligible AND enrolled in an employer-sponsored health plan or prescription drug benefit program for retirees
- Must be receiving treatment in the United States or Puerto Rico

Ask your AbbVie representative or visit **BOTOXSavingsProgram.com** for more information.

By participating in the BOTOX® Savings Program, you acknowledge and agree to the full Terms & Conditions set out at BOTOXSavingsProgram.com/TermsandConditions. Patients enrolled in Medicare, Medicaid, TRICARE, or any other government-reimbursed healthcare program are not eligible. Other restrictions and maximum limits apply.

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Primary Axillary Hyperhidrosis
The most frequently reported adverse events (3%-10% of adult patients) following injection of BOTOX for severe primary axillary hyperhidrosis in double-blind studies include injection-site pain and hemorrhage, nonaxillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

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

Summary

BOTOX® is the only botulinum toxin approved for 12 indications in the United States.

The development of BOTOX® for therapeutic use began in the 1970s with Dr. Alan B. Scott's search for a treatment that could help his patients with Strabismus, a disorder in which extraocular muscles pull the eye out of alignment. Today, 30 years after it was first approved for Blepharospasm and Strabismus, BOTOX® neurotoxin has become one of the most widely researched medications in the world. BOTOX® is approved for clinical use in ≈ 100 countries worldwide, where it serves as an important treatment for select neurologic, urologic, dermatologic, and ophthalmic conditions. The conditions for which BOTOX® treatment is approved in the United States are listed in Table 51 (BOTOX® Prescribing Information).

Table 51. BOTOX® Indications

General Condition	Indication Statement	Year of Approval
Pediatric NDO	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.	2021
Pediatric Lower Limb Spasticity	Treatment of lower limb spasticity in pediatric patients 2 to 17 years of age. **Limitations of Use** BOTOX® has not been shown to improve upper extremity functional abilities or range of motion at a joint affected by a fixed contracture.	2019*
Pediatric Upper Limb Spasticity	Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age. **Limitations of Use** BOTOX® has not been shown to improve upper extremity functional abilities or range of motion at a joint affected by a fixed contracture.	2019
Adult Lower Limb Spasticity	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). **Limitations of Use** BOTOX® has not been shown to improve upper extremity functional abilities or range of motion at a joint affected by a fixed contracture.	2016
Overactive Bladder	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.	2013
Adult Detrusor Overactivity Associated With a Neurologic Condition	Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.	2011
Chronic Migraine	Prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer). **Limitations of Use** Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.	2010

*BOTOX® was initially approved by the FDA for Pediatric Lower Limb Spasticity, excluding Spasticity caused by cerebral palsy in 2019. This marketing exclusivity was subsequently removed by the FDA in early 2020.

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

Table 51. BOTOX® Indications (continued)

General Condition	Indication Statement	Year of Approval
Adult Upper Limb Spasticity	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). **Limitations of Use** BOTOX® has not been shown to improve upper extremity functional abilities or range of motion at a joint affected by a fixed contracture.	Approved 2010 and expanded 2015
Primary Axillary Hyperhidrosis	Treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. **Limitations of Use** The safety and effectiveness of BOTOX® for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.	2004
Cervical Dystonia	Treatment of adults with Cervical Dystonia to reduce the severity of abnormal head position and neck pain associated with Cervical Dystonia.	2000
Blepharospasm	Treatment of Blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older.	1989
Strabismus	Treatment of Strabismus in patients 12 years of age and older.	1989

BOTOX® is a biological product derived from a particular strain of the organism *Clostridium botulinum*. As with many biological products, doses of onabotulinumtoxinA are given in Units of biological activity instead of weight in milligrams or nanograms. Units and Unit doses are not interchangeable among different botulinum neurotoxin products. In recognition of this, the FDA requires a statement in the Prescribing Information for each product indicating that Units are not interchangeable among different botulinum neurotoxin products. All Unit doses referred to in this monograph apply specifically to BOTOX® (BOTOX® Prescribing Information).

IMPORTANT SAFETY INFORMATION (continued)
ADVERSE REACTIONS (continued)
Postmarketing Experience
Adverse reactions that have been identified during postapproval use of BOTOX are discussed in greater detail in *Postmarketing Experience* (Section 6.3 of the Prescribing Information).

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.

In order to help distinguish among different botulinum neurotoxin products, each is required by the United States FDA to have a distinct non-proprietary name; for BOTOX®, this name is onabotulinumtoxinA. As new botulinum neurotoxin products are approved in the United States, they will be identifiable by their unique names—each of which will be associated with its own Unit-dosing recommendations.

Additionally, as a result of the heterogeneity inherent in complex biological products, efficacy and safety data are required for each individual biological product seeking regulatory approval. That is, data sets generated with any 1 biological product cannot be used in support of another product seeking regulatory approval.

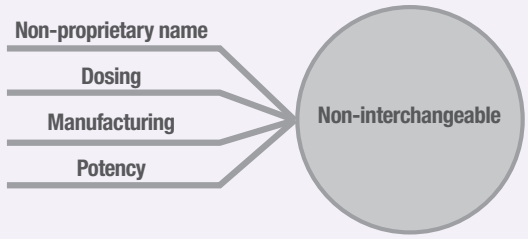


Figure 57. Botulinum toxin products differ in these areas.

Indication-specific dosage and administration recommendations should be followed. In treating adult patients for 1 or more indications, the maximum cumulative dose should not exceed 400 Units in a 3-month interval. In pediatric patients, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval.

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

Use caution when BOTOX® treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

BOTOX® is supplied in a single-dose vial. Discard any unused portion.

AbbVie is committed to educating patients and providers about BOTOX® and the disorders it is used to treat. AbbVie provides literature and other educational information to specialists such as neurologists, urologists, physiatrists (physical medicine and rehabilitation specialists), dermatologists, and ophthalmologists—the physicians most likely to see and manage the disorders for which BOTOX® is used. Through injector training and other programs, AbbVie strives to promote understanding of these conditions and to help physicians care for their patients.

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

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

Table 52. Basic Properties of BOTOX®

Botulinum toxin serotype	Type A
Non-proprietary name	onabotulinumtoxinA
Neurotoxin complex size	Homogeneous ≈ 900 kDa
Specific activity	≈ 20 Units/ng neurotoxin complex protein
Diluent	Preservative-free, sterile saline
pH reconstituted in saline	Neutral

Table 53. Additional Resources

FOR MORE INFORMATION, CALL

1-800-44-BOTOX

This telephone number will provide you with the following options after first selecting Option 2 for healthcare professionals:

OPTION **1**	Place Order/Check Order Status
OPTION **2**	BOTOX ONE® Portal Support/Patient Access
OPTION **3**	BOTOX® Savings Program
OPTION **4**	Scientific/Medical Info/Side Effects

BOTOX® Important Information

INDICATIONS

Adult 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 (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

BOTOX is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

Chronic Migraine

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

Limitations of Use

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

Spasticity

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

Limitations of Use

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

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.

Blepharospasm and Strabismus

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

Primary Axillary Hyperhidrosis

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

Limitations of Use

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, 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.

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

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and 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.

CONTRAINDICATIONS

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

BOTOX is contraindicated for intradetrusor injection in patients with a urinary tract infection, or in patients with urinary retention, or post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS

Spread of Toxin Effect

See *Boxed Warning*.

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

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.

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 preexisting 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.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hypersensitivity Reactions

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

Increased Risk of Clinically Significant Effects With Preexisting Neuromuscular Disorders

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

Dysphagia and Breathing Difficulties

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

Pulmonary Effects of BOTOX in Patients With Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated With a Neurologic Condition

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

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.

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.

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units to 360 Units total dose) compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

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

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

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

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

Urinary Tract Infections in Patients With Overactive Bladder

BOTOX increases the incidence of UTI. 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.

Urinary Retention in Adults Treated for Bladder Dysfunction

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

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

Overactive Bladder

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

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

Adult Detrusor Overactivity Associated With a Neurologic Condition

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

Among adult patients not using CIC at baseline, those with multiple sclerosis were more likely to require CIC postinjection than those with spinal cord injury.

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

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.

ADVERSE REACTIONS

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

Overactive Bladder

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

A higher incidence of UTI was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than nondiabetics.

The incidence of UTI increased in patients who experienced a maximum PVR urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% vs 23%, respectively.

Adult Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions within 12 weeks of BOTOX injection for detrusor overactivity associated with a neurologic condition include UTI (BOTOX 24%, placebo 17%); urinary retention (BOTOX 17%, placebo 3%); and hematuria (BOTOX 4%, placebo 3%).

The following adverse event rates were reported at any time following initial injection and prior to reinjection or study exit (median duration of 44 weeks of exposure): UTIs (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

Pediatric Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions during the 12 weeks following BOTOX injection of 200 Units for pediatric detrusor overactivity associated with a neurologic condition include bacteriuria (20%), UTI (7%), leukocyturia (7%), and hematuria (3%).

The most common adverse reactions in patients who received BOTOX 6 Units/kg and less than a total dose of 200 Units were UTI, bacteriuria, and hematuria.

These patients were not adequately managed with at least one anticholinergic agent and were using CIC at baseline.

Chronic Migraine

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

Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in study 1 and study 2, usually within the first week after treatment, compared with 0.3% of placebo-treated patients.

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

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS (continued)

Adult Upper Limb Spasticity

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

Adult 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.

Pediatric Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric upper limb spasticity include upper respiratory tract infection (includes upper respiratory tract infection and viral upper respiratory tract infection), injection-site pain, nausea, constipation, rhinorrhea, nasal congestion, and seizure (includes seizure and partial seizure).

Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric lower limb spasticity include injection-site erythema, injection-site pain, oropharyngeal pain, ligament sprain, skin abrasion, and decreased appetite.

Cervical Dystonia

The most frequently reported adverse reactions following injection of BOTOX for cervical cystonia include dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Blepharospasm

The most frequently reported adverse reactions following injection of BOTOX for blepharospasm include ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Strabismus

The most frequently reported adverse events following injection of BOTOX for strabismus include ptosis (1% after inferior rectus injections, 16% after horizontal rectus injections, and 38% after superior rectus injections) and vertical deviation (17%).

Primary Axillary Hyperhidrosis

The most frequently reported adverse events (3%-10% of adult patients) following injection of BOTOX for severe primary axillary hyperhidrosis in double-blind studies include injection-site pain and hemorrhage, nonaxillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

Postmarketing Experience

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

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

DRUG INTERACTIONS

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

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide, or visit https://www.rxabbvie.com/pdf/botox_pi.pdf

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