# PrBOTOX®

onabotulinumtoxinA for injection Ph. Eur.

***Clostridium botulinum* type A neurotoxin complex (900kD)**

**Sterile vacuum-dried concentrate powder for solution for injection**

**50, 100 and 200 Allergan units per vial**

**Neuromuscular Paralytic Agent**

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# PART I: HEALTH PROFESSIONAL INFORMATION

## SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| • Intramuscular Use for All Indications except Hyperhidrosis and Bladder Dysfunction<br>• Intradetrusor Use for Bladder Dysfunction only<br>• Intradermal Use for Hyperhidrosis only | Sterile vacuum-dried concentrate; powder for solution for injection; 50, 100 and 200 Allergan units per vial | Albumin (human)<br>*For a complete listing see Dosage Forms, Composition and Packaging section.* |

## INDICATIONS AND CLINICAL USE

BOTOX® (onabotulinumtoxinA for injection) is indicated:

**Blepharospasm**

- for the treatment of blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age or older,

**Strabismus**

- for the treatment of strabismus in patients 12 years of age or older. BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair,

**Cervical Dystonia (spasmodic torticollis)**

- to reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults,

**Focal Spasticity**

- in the management of focal spasticity, including the treatment of upper limb spasticity associated with stroke in adults,
- for the symptomatic treatment of lower limb spasticity associated with stroke in adults.

**Equinus Foot**

- in the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients, two years of age or older,

**Primary Hyperhidrosis of the Axillae**

- for the treatment of hyperhidrosis of the axilla in patients 18 years of age or older,

**Chronic Migraine**

- for the prophylaxis of headaches in adults with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer),

**Bladder Dysfunction**

**Neurogenic Detrusor Overactivity associated with a neurological condition**

- for the treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from neurogenic bladder associated with multiple sclerosis or subcervical spinal cord injury in adults who had an inadequate response to or are intolerant of anticholinergic medications.

**Overactive Bladder**

- for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.

**Geriatrics (> 65 years of age):**

Studies specifically designed to determine the dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. Initial dosing should begin at the lowest recommended dose for the specific indication.

The safety and effectiveness of BOTOX® in the prophylaxis of headaches in chronic migraine has not been investigated in subjects over 65 years of age.

Of 1242 patients in placebo-controlled clinical studies of BOTOX® for the treatment of overactive bladder, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. No overall difference in the safety profile following BOTOX® treatment was observed between patients aged 65 years and older compared to younger patients in these studies, with the exception of urinary tract infection where the incidence was higher in patients 65 years of age or older in both the placebo and BOTOX® groups compared to the younger patients. Similarly, no overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical studies.

**Pediatrics (< 18 years of age):**

The safety and effectiveness of BOTOX® in the treatment of blepharospasm or strabismus have not been investigated in children under 12 years of age.

The safety and effectiveness of BOTOX® in the treatment of cervical dystonia has not been investigated in children under 16 years of age.

The safety and effectiveness of BOTOX® in the management of focal spasticity, including the treatment of upper and lower limb spasticity associated with stroke has not been investigated in

children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients has not been investigated in children under two years of age.

The safety and effectiveness of BOTOX® in the prophylaxis of headaches in chronic migraine has not been investigated in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of hyperhidrosis of the axilla has not been investigated in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to neurogenic detrusor overactivity have not been established in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to overactive bladder have not been established in patients below the age of 18 years.

## CONTRAINDICATIONS

BOTOX® is contraindicated in:

- patients who are hypersensitive to any botulinum toxin type A or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- the presence of infection at the proposed injection site(s).

BOTOX® for the treatment of bladder dysfunction is also contraindicated in:

- patients who have a urinary tract infection or a recent history of frequent urinary tract infections.
- patients with urinary retention who are not routinely catheterizing.
- patients who are not willing and able to have clean intermittent catheterization (CIC) initiated.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- The term "Allergan unit" upon which dosing is based is a specific measurement of toxin activity that is unique to Allergan's formulation of botulinum toxin type A. Therefore, the "Allergan units" used to describe BOTOX® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX® activity are not interchangeable with other products.
- BOTOX® should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.
- Follow the recommended dosage and frequency of administration for BOTOX® (See **WARNINGS AND PRECAUTIONS**, **General** and **DOSAGE AND ADMINISTRATION**).
- DISTANT SPREAD OF TOXIN EFFECT: 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 occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

### General

Use BOTOX® only as directed.

Do not use dosage recommendations and potency Units applied to other botulinum toxin products when using BOTOX®.

The safe and effective use of BOTOX® (onabotulinumtoxinA for injection) depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.

Physicians administering BOTOX® should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. An understanding of standard electromyographic techniques is also required for treatment of strabismus, and may be useful for the treatment of cervical dystonia, and focal spasticity associated with pediatric cerebral palsy and upper and lower limb spasticity in adults.

Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

Caution should be used when BOTOX® 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.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported.

Progressive signs or symptoms of muscular weakness remote to the site of injection may include ptosis and diplopia, as well as other serious adverse effects including swallowing and speech disorders, generalized weakness or respiratory failure. In addition, certain adverse effects (e.g., dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, some of which have been associated with a fatal outcome.

When exposed to very high doses, patients with neurologic disorders, e.g. pediatric cerebral palsy or adult spasticity, may be at increased risk of clinically significant systemic effects.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Patients with a history of underlying neurological disorders, dysphagia and/or aspiration should be treated with extreme caution. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk.

Injection specific dosage and administration recommendations should be followed. In treating adult patients, including when combining indications, the maximum cumulative dose in a 3 month interval should generally not exceed 7 U/kg or 400 Units, whichever is lower. In treating pediatric patients, the maximum cumulative dose in a 3 month interval should generally not exceed 6 Units/kg or 200 Units, whichever is lower.

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

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

*Focal Spasticity and Equinus Foot*
BOTOX® is a treatment of spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX® is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

BOTOX® should be used for the treatment of focal lower limb spasticity in adult post-stroke patients only if muscle tone reduction is expected to result in improved function (e.g., improvement in gait), or improved symptoms (e.g. reduction in pain), or to facilitate care.

Caution should be exercised when treating adult patients with post-stroke spasticity who may be at increased risk of fall.

BOTOX® should be used with caution for the treatment of focal lower limb spasticity in elderly post-stroke patients with significant co-morbidity and treatment should only be initiated if the benefit of treatment is considered to outweigh the potential risk.

*Chronic Migraine*
No efficacy has been shown for BOTOX® in the prophylaxis of headaches in patients with episodic migraine (< 15 headache days per month).

*Bladder Dysfunction*
Appropriate medical caution should be exercised for performing a cystoscopy.

Patients who are not catheterizing prior to treatment may subsequently require catheterization for urinary retention. In patients who are not catheterizing, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks. Patients should be instructed to contact their physician if they experience difficulties in voiding.

*Neurogenic Detrusor Overactivity*
In these patients, autonomic dysreflexia associated with the procedure could occur, which may require prompt medical therapy.

Patients with spinal cord injury above T1 were excluded from BOTOX® clinical trials for neurogenic detrusor overactivity.

**Carcinogenesis and Mutagenesis**

Studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX®. BOTOX® was not mutagenic in *in vitro* and *in vivo* mutagenicity studies. (See TOXICOLOGY Section for more information.)

**Cardiovascular**

There have been reports following administration of botulinum toxin of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal

outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. The exact relationship of these events to BOTOX®/BOTOX COSMETIC® is unknown.

**Ear/Nose/Throat**

*Cervical Dystonia* - Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all types of botulinum toxins. Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be mild, but could be severe. Consequent to the dysphagia there is the potential for aspiration, dyspnea and occasionally the need for tube feeding. In rare cases, dysphagia followed by aspiration pneumonia and death has been reported.

Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia has contributed to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX® injection.

Limiting the dose injected into both sternocleidomastoid muscles to less than 100 units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the localized diffusion of the toxin to the oesophageal musculature.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

**Immune**

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

As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent for BOTOX® and consequently the causal agent cannot be reliably determined. If such a reaction

occurs, further injection should be discontinued and appropriate medical therapy initiated immediately.

**Neurologic**

Extreme caution should be exercised when administering BOTOX® to individuals with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX®. There have been rare cases of administration of botulinum toxin to patients with known or unrecognized neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. **When exposed to very high doses, patients with neurologic disorders, e.g. pediatric cerebral palsy or adult spasticity, may also be at increased risk of clinically significant systemic effects.**

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The reports in children were reports predominantly from cerebral palsy patients treated for spasticity. The exact relationship of these events to the botulinum toxin injection has not been established**.**

**Ophthalmologic**

*Blepharospasm* - Reduced blinking following BOTOX® injection into the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. One case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles. Acute angle closure glaucoma has been reported very rarely following periorbital injections of botulinum toxin.

*Strabismus* - BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist contracture in conjunction with surgical repair. The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. In order to enhance efficacy, multiple injections over time may be required.

During the administration of BOTOX® for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible.

Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available.

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms.

**Skin**

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

*Primary hyperhidrosis of the axillae* - Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism or phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Special Populations**

**Pregnant Women:** There are no adequate and well-controlled studies of BOTOX® administration in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. BOTOX® should not be used during pregnancy unless clearly necessary. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

**Nursing Women:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX® is administered to a nursing woman.

**Pediatrics** (2-18 years of age): **There have been very rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. A causal association to BOTOX® has not been established in these cases. Post-marketing reports of possible distant spread of toxin have been very rarely reported in pediatric patients with co-morbidities, predominantly with cerebral palsy, who received > 8 U/kg. Extreme caution should be exercised when treating pediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.**

The safety and effectiveness of BOTOX® in the prophylaxis of headaches in chronic migraine has not been investigated in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of blepharospasm or strabismus have not been investigated in children under 12 years of age.

The safety and effectiveness of BOTOX® in the treatment of cervical dystonia has not been investigated in children under 16 years of age.

The safety and effectiveness of BOTOX® in the management of focal spasticity, including upper and lower limb spasticity associated with stroke and primary hyperhidrosis of the axillae, has not been investigated in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients has not been investigated in children under two years of age.

The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to neurogenic detrusor overactivity have not been established in children and adolescents under 18 years of age.

The safety and effectiveness of BOTOX® in the treatment of urinary incontinence due to overactive bladder have not been established in patients below the age of 18 years.

**Geriatrics (> 65 years of age)**: Studies of BOTOX® specifically designed to determine dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. In addition, aggregate review of BOTOX® postmarketing and clinical trial safety reports showed that, in general, the risk of adverse events is comparable between the elderly and younger population. In general, dose selection for an elderly patient should be cautious, usually starting at the lowest recommended dose for the specific indication.

Of 1242 patients in placebo-controlled clinical studies of BOTOX® for the treatment of overactive bladder, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. No overall difference in the safety profile following BOTOX® treatment was observed between patients aged 65 years and older compared to younger patients in these studies, with the exception of urinary tract infection where the incidence was higher in patients 65 years of age or older in both the placebo and BOTOX® groups compared to the younger patients. Similarly, no overall difference in effectiveness was observed between these age groups in placebo-controlled pivotal clinical studies.

### Monitoring and Laboratory Tests

There are no specific requirements for laboratory test monitoring when patients are treated with BOTOX®.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

In general, adverse reactions occur within the first few days following injection and while generally transient may have duration of several months or, in rare cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported. Muscle weakness remote to the site of injection and other serious adverse effects (e.g. dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, some associated with a fatal outcome.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, tenderness, swelling/oedema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

For each indication the frequency of adverse reactions documented during clinical trials is given. The following lists events that occurred in ≥ 1% of subjects. The frequency is defined as follows: Very Common (≥ 1/10); Common (≥1/100, <1/10).

***Blepharospasm***

Safety data compiled from controlled clinical trials and open label studies involving 1732 patients treated with BOTOX®, the following adverse reactions were reported.

| | |
|---|---|
| ***Eye disorders*** | |
| Very common | Eyelid ptosis |
| Common | Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, lacrimation increase |
| ***Skin and subcutaneous tissue disorder*** | |
| Common | Ecchymosis |

***Strabismus***

Safety data compiled from clinical trials involving approximately 2058 patients treated with BOTOX®, the following adverse reactions were reported.

| | |
|---|---|
| ***Eye disorders*** | |
| Very common | Eyelid ptosis, eye movement disorder |

***Cervical dystonia***

Safety data compiled from placebo controlled, double-blind trial involving 231 patients treated with BOTOX®, the following adverse reactions were reported.

| | |
|---|---|
| ***Infections and infestations*** | |
| Common: | Rhinitis, upper respiratory tract infection |

| | |
|---|---|
| ***Nervous system disorders*** | |
| Common: | Dizziness, hypertonia, hypoesthesia, somnolence, headache |
| ***Gastrointestinal disorders*** | |
| Very common: | Dysphagia |
| Common: | Dry mouth, nausea |
| ***Musculoskeletal and connective tissue disorders*** | |
| Very common: | Muscular weakness |
| Common: | Musculoskeletal stiffness |
| ***General disorders and administration site conditions*** | |
| Very common: | Pain |
| Common: | Asthenia, malaise, influenza like illness |

***Equinus foot***

Safety data compiled from two double-blind, randomized, placebo controlled and an open-label extension studies involving approximately 304 patients treated with BOTOX®. The following adverse reactions were reported.

| | |
|---|---|
| ***Infections and infestations*** | |
| Very common: | Viral infection, ear infection |
| ***Nervous system disorders*** | |
| Common: | Somnolence, gait disturbance, paresthesia |
| ***Skin and subcutaneous tissue disorders*** | |
| Common: | Rash |
| ***Musculoskeletal and connective tissue disorders*** | |
| Common: | Myalgia, muscular weakness, pain in extremity |
| ***Renal and urinary disorders*** | |
| Common: | Urinary incontinence |
| ***Injury, poisoning and procedural complications*** | |
| Common: | Fall |
| ***General disorders and administration site conditions*** | |
| Common: | Malaise, injection site pain, asthenia |

***Focal Spasticity***

***Upper Limb:***

Safety data compiled from double-blind and open label studies involving 339 patients treated with BOTOX®. The following adverse reactions were reported.

| | |
|---|---|
| ***Nervous system disorders*** | |
| Common: | Hypertonia |
| ***Skin and subcutaneous tissue disorders*** | |
| Common: | Ecchymosis |
| ***Musculoskeletal and connective tissue disorders*** | |
| Common: | Muscular weakness, pain in extremity |
| ***General disorders and administration site conditions*** | |
| Common: | Injection site pain, pyrexia, influenza like illness |

***Lower Limb:***
A total of 538 adult patients have been treated with Botox® for lower limb spasticity in 7 double-blind, placebo-controlled studies.

The most frequently reported adverse events in patients treated in the All BOTOX group were fall (which occurred in 4.5% and 4.5% in Botox® groups and placebo groups, respectively) and pain in extremity (which occurred in 5.0% and 4.7% in Botox® groups and placebo groups, respectively).

**Adverse Reactions Reported in ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb spasticity – A Single Dose Placebo-Controlled Study (First 12 Weeks of Double-blind Phase)**

| **Adverse Reactions** | **Number (%) of Patients** | |
|---|---|---|
| | **BOTOX (300 -400U) (N=231)** | **Placebo (N=233)** |
| Musculosceletal and connective tissue disorders | | |
| Arthralgia | 8 (4%) | 2 (1%) |
| Back Pain | 6 (3%) | 4 (2%) |
| Myalgia | 4 (2%) | 3 (1%) |
| Infections and infestations | | |
| Upper respiratory tract infection | 4 (2%) | 2 (1%) |
| General Disorder and administration site condition | | |
| Injection site pain | 5 (2%) | 3 (1%) |

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

***Primary hyperhidrosis of the axillae***
Safety data compiled from double-blind and open- label studies involving 397 patients treated with BOTOX®. The following adverse reactions were reported.

| | |
|---|---|
| ***Nervous system disorders*** | |
| Common: | Headache, paresthesia |
| ***Vascular disorders*** | |
| Common: | Hot flush |
| ***Gastrointestinal disorders*** | |
| Common: | Nausea |
| ***Skin and subcutaneous tissue disorders*** | |
| Common: | Hyperhidrosis, skin odor abnormal, pruritus, subcutaneous nodule, alopecia |
| ***Musculoskeletal and connective tissue disorders*** | |
| Common: | Pain in extremity |

| ***General disorders and administration site conditions*** | |
|---|---|
| Very common: | Injection site pain |
| Common: | Pain, injection site edema, injection site hemorrhage, injection site hypersensitivity, injection site irritation, asthenia |

Note: increase in non-axillary sweating was reported in 4.5% of patients within one month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

***Chronic Migraine***

Safety data compiled from two chronic migraine double-blind, placebo controlled phase 3 clinical trials involving 687 patients treated with BOTOX®. The following adverse reactions were reported.

**Adverse Reactions Reported by ≥ 2% of BOTOX® Treated Patients and More Frequent than in Placebo-treated Patients in Two Phase 3 Chronic Migraine Double-blind, Placebo-controlled Clinical Trials**

| **System Organ Class/ Preferred Term** | **BOTOX ® (N = 687)** | **Placebo (N = 692)** |
|---|---|---|
| **OVERALL** | 429 (62.4%) | 358 (51.7%) |
| ***Eye Disorders*** | | |
| Eyelid ptosis | 25 (3.6%) | 2 (0.3%) |
| ***General Disorders & Administration Site Conditions*** | | |
| Injection site pain | 23 (3.3%) | 14 (2.0%) |
| ***Infections & Infestations*** | | |
| Sinusitis | 28 (4.1%) | 27 (3.9%) |
| Bronchitis | 17 (2.5%) | 11 (1.6%) |
| ***Musculoskeletal & Connective Tissue Disorders*** | | |
| Neck pain | 60 (8.7%) | 19 (2.7%) |
| Musculoskeletal stiffness | 25 (3.6%) | 6 (0.9%) |
| Muscular weakness | 24 (3.5%) | 2 (0.3%) |
| Myalgia | 21 (3.1%) | 6 (0.9%) |
| Musculoskeletal pain | 18 (2.6%) | 10 (1.4%) |
| ***Nervous System Disorders*** | | |
| Headache | 32 (4.7%) | 22 (3.2%) |
| Migraine | 26 (3.8%) | 18 (2.6%) |
| Facial paresis | 15 (2.2%) | 0 (0.0%) |

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX® vs. 1.2% for placebo. The most frequently reported adverse events leading to discontinuation in the BOTOX® group were neck pain (0.6%), muscular weakness (0.4%), headache (0.4%), and migraine (0.4%).

***Neurogenic Detrusor Overactivity associated with a neurologic condition***

The table below presents the most frequently reported adverse reactions in two double-blind, placebo-controlled studies with BOTOX® 200 Units within 12 weeks of injection for detrusor overactivity associated with a neurologic condition.

**Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection in Two Double-blind, Placebo-controlled Clinical Trials**

| **Adverse Reactions by System Organ Class** | **BOTOX® 200 Unit (N=262)** | **Placebo (N=272)** |
|---|---|---|
| Infections and infestations | | |
| Urinary tract infection | 64 (24%) | 47 (17%) |
| Renal and urinary disorders | | |
| Urinary retention | 45 (17%) | 8 (3%) |
| Hematuria | 10 (4%) | 8 (3%) |
| General disorders and administration site conditions | | |
| Fatigue | 10 (4%) | 3 (1%) |
| Psychiatric disorders | | |
| Insomnia | 4 (2%) | 0 (0%) |

The following adverse event rates 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%), fatigue (6%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), insomnia (3%), and muscle spasm (2%).

In the multiple sclerosis (MS) patients enrolled in the pivotal studies, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX® and 0.20 for placebo.

Among patients who were not catheterizing at baseline prior to treatment, catheterization was initiated in 38.9% following treatment with BOTOX® 200 Units versus 17.3% on placebo. Catheterization rates by etiology (multiple sclerosis [MS] and spinal cord injury [SCI]) are further presented in the table below.

**Proportion of Patients by Etiology (MS and SCI) not Using CIC at Baseline and then Initiating Catheterization following Injection at Any Time During the Complete Treatment Cycle in Two Double-blind, Placebo-controlled Clinical Trials**

| | MS | | SCI | |
|---|---|---|---|---|
| | **BOTOX® 200 Unit (N=86)** | **Placebo (N=88)** | **BOTOX® 200 Unit (N=22)** | **Placebo (N=16)** |
| CIC initiated for any reason | 34 (40%) | 15 (17%) | 8 (36%) | 3 (19%) |
| CIC initiated for urinary retention | 27 (31%) | 4 (5%) | 6 (27%) | 3 (19%) |

In these clinical trials, no change in the type of adverse reactions was observed following two treatments.

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

***Post-Approval Commitment Study***

A placebo-controlled, double-blind post-approval study with BOTOX® 100 Units was conducted in Multiple Sclerosis (MS) patients with urinary incontinence due to neurogenic detrusor overactivity. These patients were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. The table below presents the most frequently reported adverse reactions within 12 weeks of injection.

**Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection**

| **Adverse Reactions by System Organ Class** | **BOTOX® 100 Unit (N=66)** | **Placebo (N=78)** |
|---|---|---|
| Infections and infestations | | |
| Urinary tract infection | 17 (26%) | 5 (6%) |
| Bacteriuria | 6 (9%) | 4 (5%) |
| Renal and urinary disorders | | |
| Urinary retention | 10 (15%) | 1 (1%) |
| Dysuria | 3 (5%) | 1 (1%) |
| Investigations | | |
| Residual urine volume* | 11 (17%) | 1 (1%) |

* Elevated PVR not requiring catheterization

The following adverse event rates with BOTOX® 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of 51 weeks of exposure): urinary tract infections (39%), bacteriuria (18%), urinary retention (17%), residual urine volume* (17%), dysuria (9%), and hematuria (5%).

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

Catheterization was initiated in 15.2% of patients following treatment with BOTOX® 100 Units versus 2.6% on placebo.

***Overactive Bladder***

The table below presents the most frequently reported adverse reactions in double-blind, placebo-controlled, pivotal Phase 3 studies within 12 weeks of injection for overactive bladder.

**Adverse Reactions Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks, in Double-blind, Placebo-controlled, Pivotal Phase 3 Clinical Trials**

| Adverse Reactions by System Organ Class | BOTOX® 100 Unit (N=552) | Placebo (N=542) |
|---|---|---|
| Infections and infestations | | |
| Urinary tract infection | 99 (18%) | 30 (6%) |
| Bacteriuria | 24 (4%) | 11 (2%) |
| Renal and urinary disorders | | |
| Dysuria | 50 (9%) | 36 (7%) |
| Urinary retention | 31 (6%) | 2 (0%) |
| Investigations | | |
| Residual urine volume* | 17 (3%) | 1 (0%) |

*****Elevated PVR not requiring catheterization

During the complete treatment cycle, the following adverse reactions with BOTOX® 100 Units were reported: urinary tract infections (26%), dysuria (11%), bacteriuria (8%), urinary retention (6%), residual urine volume (3%), and pollakiuria (2%).

Events considered to be procedure-related by the investigator reported at any time following initial injection were dysuria (6%) and haematuria (2%).

Catheterization was initiated in 6.5% following treatment with BOTOX® 100 Units versus 0.4% in the placebo group.

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

**Less Common Clinical Trial Adverse Drug Reactions (<1%)**

For each indication the frequency of adverse reactions documented during clinical trials is given. The frequency is defined as follows: Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000).

***Blepharospasm***

| | |
|---|---|
| ***Nervous system disorders*** | |
| Uncommon | Dizziness, facial palsy |
| ***Eye disorders*** | |
| Uncommon | Keratitis, ectropion, diplopia, entropion, vision blurred. |

| | |
|---|---|
| Rare | Eyelid edema. |
| Very rare | Ulcerative keratitis, corneal epithelium defect, corneal perforation |
| ***Skin and subcutaneous tissue disorder*** | |
| Uncommon | Rash |
| ***General disorders and administration site conditions*** | |
| Uncommon | Fatigue |

***Strabismus***

| ***Eye disorders*** | |
|---|---|
| Uncommon | Ocular retrobulbar hemorrhages, eye penetration, Holmes-Adie pupil |
| Rare | Vitreous hemorrhage |

***Cervical dystonia***

| ***Eye disorders*** | |
|---|---|
| Uncommon | Diplopia, eyelid ptosis |
| ***General disorders and administration site conditions*** | |
| Uncommon | Pyrexia |

***Focal Spasticity***

| ***Nervous system disorders*** | |
|---|---|
| Uncommon: | Hypoesthesia, headache, paresthesia |
| ***Vascular disorders*** | |
| Uncommon: | Orthostatic hypotension |
| ***Gastrointestinal disorders*** | |
| Uncommon: | Nausea |
| ***Skin and subcutaneous tissue disorders*** | |
| Uncommon: | Dermatitis, pruritis, rash |
| ***Musculoskeletal and connective tissue disorders*** | |
| Uncommon: | Arthralgia, bursitis |
| ***General disorders and administration site conditions*** | |
| Uncommon: | Asthenia, pain, injection site hypersensitivity, malaise |

***Chronic Migraine***

| ***Gastrointestinal disorders*** | |
|---|---|
| Uncommon: | Dysphagia |
| ***Skin and subcutaneous tissue disorders*** | |
| Uncommon: | Pain of skin |
| ***Musculoskeletal and connective tissue disorders*** | |
| Uncommon: | Pain in jaw |

**Abnormal Hematologic and Clinical Chemistry Findings**

No specific trends in abnormal hematologic or clinical chemistry findings have been reported.

**Post-Market Adverse Drug Reactions**

BOTOX® and BOTOX COSMETIC® contain the same active ingredient in the same

formulation. Therefore, adverse events observed with the use of BOTOX COSMETIC® also have the potential to be associated with the use of BOTOX®.

Adverse events after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with dysphagia, respiratory compromise, pneumonia, and/or other significant debility. 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 pre-existing cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The reports in children were predominantly from cerebral palsy patients treated for spasticity. The exact relationship of these events to the botulinum toxin injection has not been established.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX® inappropriately diluted with 5 ml of 1% lidocaine. The causal role of BOTOX®, lidocaine, or both cannot be reliably determined.

The following list of adverse drug reactions or other medically relevant adverse events have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in the WARNING AND PRECAUTIONS, and Clinical Trials Adverse Drug Reactions sections: denervation/muscle atrophy; respiratory depression and/or respiratory failure; dyspnea; aspiration pneumonia; dysarthria; dysphonia; dry mouth; strabismus; peripheral neuropathy; abdominal pain; diarrhea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance, hypoacusis; tinnitus; vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoesthesia; malaise; myalgia; myasthenia gravis; paresthesia; allergic reaction, skin rash (including erythema multiforme, urticaria, dermatitis psoriasiform and psoriasiform eruption); pruritus; hyperhidrosis; alopecia, including madarosis; worsening of migraine; dry eye; localized muscle twitching/involuntary muscle contractions.

Angle closure glaucoma has been reported very rarely following BOTOX® treatment for blepharospasm.

These reactions are reported voluntarily from a population of uncertain size. The exact relationship of these events to botulinum toxin is unknown.

## DRUG INTERACTIONS

### Overview

No specific interactions have been reported.

### Drug-Drug Interactions

| Table 1: Established or Potential Drug-Drug Interactions | | | |
|---|---|---|---|
| **Proper name of drug** | **Ref** | **Effect** | **Clinical comment** |
| aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents, both depolarizing (succinylcholine) and non-depolarizing (tubocurarine derivatives), lincosamides, polymyxins, quinidine, magnesium sulfate, and anticholinesterases). | T | Theoretically, the effect of botulinum toxin type A may be potentiated | The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other drugs that interfere with neuromuscular transmission (e.g. tubocuraine-type muscle relaxants). Caution should be exercised when BOTOX® is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs that interfere with neuromuscular transmission. |
| Different botulinum neurotoxin serotypes | T | Unknown | The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. |

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### Drug-Food Interactions

Interactions with food have not been established.

### Drug-Herb Interactions

Interactions with herbal products have not been established.

### Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- **Intramuscular Use for All Indications except Hyperhidrosis and Bladder Dysfunction**
- **Intradetrusor Use for Bladder Dysfunction only**
- **Intradermal Use for Hyperhidrosis only**

    - BOTOX® **(**onabotulinumtoxinA for injection) should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.

- The term "Allergan unit" upon which dosing is based, is a specific measurement of toxin activity that is unique to Allergan's formulation of botulinum toxin type A. Therefore, the "Allergan units" used to describe BOTOX® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX® activity are not interchangeable with other products.

- The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative.

- Follow the recommended dosage and frequency of administration for each indication.

    - Generally, optimum dose levels and the number of injection sites per muscle have not been established for all indications. The exact dosage and number of injection sites should be tailored to the patient's needs based on the size, number and location of muscles involved, the severity of disease, presence of local muscle weakness, response to previous treatment, and the patient's medical condition. Treatment should be initiated at the lowest effective dose. This dose can be gradually increased in subsequent treatments to the maximum recommended dose, if needed.

    - Injection intervals of BOTOX® should be according the specific indication. In treating adult patients, when combining indications, the maximum cumulative dose in a 3 month interval should generally not exceed 7 Units/kg, or 400 Units, whichever is lower. In treating pediatric patients, the maximum cumulative dose in a 3 month interval should generally not exceed 6 Units/kg body weight, or 200 Units, whichever is lower.

### Recommended Dose and Dosage Adjustment

#### *Blepharospasm*

For blepharospasm, diluted BOTOX® (see Dilution Table 6) is injected using a sterile, 27 - 30 gauge needle with or without electromyographic guidance. The initial recommended dose is 1.25 U to 2.5 U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Treatment effects last approximately three months, following which the procedure can be repeated indefinitely.

The initial dose should not exceed 25 Units per eye. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient (i.e., defined as an effect that lasts no longer than two months). However there appears to be little benefit obtainable from injecting more than 5.0 U per site. Some tolerance may be found when BOTOX® is used in treating blepharospasm if treatments are given more frequently than every three months, and it is rare to have the effect be permanent.

The cumulative dose of BOTOX® for treatment of blepharospasm in a two month period should not exceed 200 U.

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.

***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 techniques.

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.

*Note:* The recommended volume of BOTOX® injected for treatment of strabismus is 0.05 mL to 0.15 mL per muscle.

The initial listed doses of the diluted BOTOX® (see Dilution Table 6) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare.

About one-half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

I. Initial doses in units (abbreviated as U). Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

   A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 U to 2.5 U in any one muscle.

B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 U to 5.0 U in any one muscle.

C. For persistent VI nerve palsy of one month or longer duration: 1.25 U to 2.5 U in the medial rectus muscle.

II. Subsequent doses for residual or recurrent strabismus.

A. It is recommended that patients be reexamined 7-14 days after each injection to assess the effect of that dose.

B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.

C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.

D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.

E. The maximum recommended dose as a single injection for any one muscle is 25 U.

F. The recommended volume of BOTOX® injected for treatment of strabismus is 0.05mL to 0.15 mL per muscle.

***Cervical dystonia (spasmodic torticollis)***

Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX®. Dosing must be tailored to the individual patient based on the patient's head and neck position, localization of pain and muscle hypertrophy, patient's bodyweight, and patient response. In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of diluted BOTOX® ranged from 140 U to 280 U. However, in clinical practice, a range of 200 U to 360 U have been used effectively.

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. For cervical dystonia, localization of the involved muscles with electromyographic guidance may be useful.

Multiple injection sites allow BOTOX® to have more uniform contact with the innervation areas of the dystonic muscle, and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes, but not more frequently than every two months. The interval between injections reported in the clinical trials showed

substantial variation (from 2 to 32 weeks), with a typical duration of approximately 12 to 16 weeks, depending on patient's individual symptoms and responses.

The maximum cumulative dose for cervical dystonia should not generally exceed 360 Units in a 3 month interval.

**Table 2 is intended to give dosing guidelines for injection of BOTOX® in the treatment of cervical dystonia.**

| Table 2: Dosage Guide for Cervical dystonia | | |
|---|---|---|
| **Classification** | **Muscle Groupings** | **Total Dosage; Number of Sites** |
| Type I<br>Head rotated toward side of shoulder elevations | Sternocleidomastoid<br>Levator scapulae<br>Scalene<br>Splenius capitis<br>Trapezius | 50-100 U; at least 2 sites<br>50 U; 1-2 sites<br>25-50 U; 1-2 sites<br>25-75 U; 1-3 sites<br>25-100 U; 1-8 sites |
| Type II<br>Head rotation only | Sternocleidomastoid | 25-100 U; at least 2 sites if >25 U given |
| Type III<br>Head tilted toward side of shoulder elevation | Sternocleidomastoid<br>Levator scapulae<br>Scalene<br>Trapezius | 25-100 U; at posterior border; at least 2 sites if >25 U given<br>25-100 U; at least 2 sites<br>25-75 U; at least 2 sites<br>25-100 U; 1-8 sites |
| Type IV<br>Bilateral posterior cervical muscle spasm with elevation of the face | Splenius capitis and cervicis | 50-200 U; 2-8 sites, treat bilaterally |

This information is provided as guidance for the initial injection. The extent of muscle hypertrophy and the muscle groups involved in the dystonic posture may change with time necessitating alterations in the dose of toxin and muscles to be injected. The exact dosage and sites injected must be individualized for each patient.

***Focal Spasticity***

***Upper Limb:***

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. In clinical trials, the doses did not exceed 360 U divided among selected muscles (typically in the flexor muscles of the elbow, wrist and fingers) at any treatment session.

Table 3 is intended to give dosing guidelines for injection of BOTOX® in the treatment of upper limb spasticity associated with stroke.

| **Table 3: Dosing guidelines in upper limb spasticity associated with stroke** | |
|---|---|
| **Muscle** | **Total Dosage; Number of Sites** |
| Biceps brachii | 100 - 200 U; up to 4 sites |
| Flexor digitorum profundus | 15 - 50 U; 1-2 sites |
| Flexor digitorum sublimis | 15 - 50 U; 1-2 sites |
| Flexor carpi radialis | 15 - 60 U; 1-2 sites |
| Flexor carpi ulnaris | 10 - 50 U; 1-2 sites |
| Adductor Pollicis | 20 U; 1-2 sites |
| Flexor Pollicis Longus | 20 U**;** 1-2 sites |

In controlled and open non-controlled clinical trials doses usually between 200 and 240 units, and up to 360 units divided among selected muscles have been used at a given treatment session.

In controlled clinical trials patients were followed for 12 weeks after single treatment. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most of the patients were re- injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 units over 54 weeks. If it is deemed appropriate by the treating physician, repeat doses may be administered, when the effect of a previous injection has diminished. Re-injections should not occur before 12 weeks. The degree and pattern of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX® and muscles to be injected. The lowest effective dose should be used.

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22-gauge needle may be used for deeper musculature. For focal spasticity, localization of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful.

Multiple injection sites allow BOTOX® to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

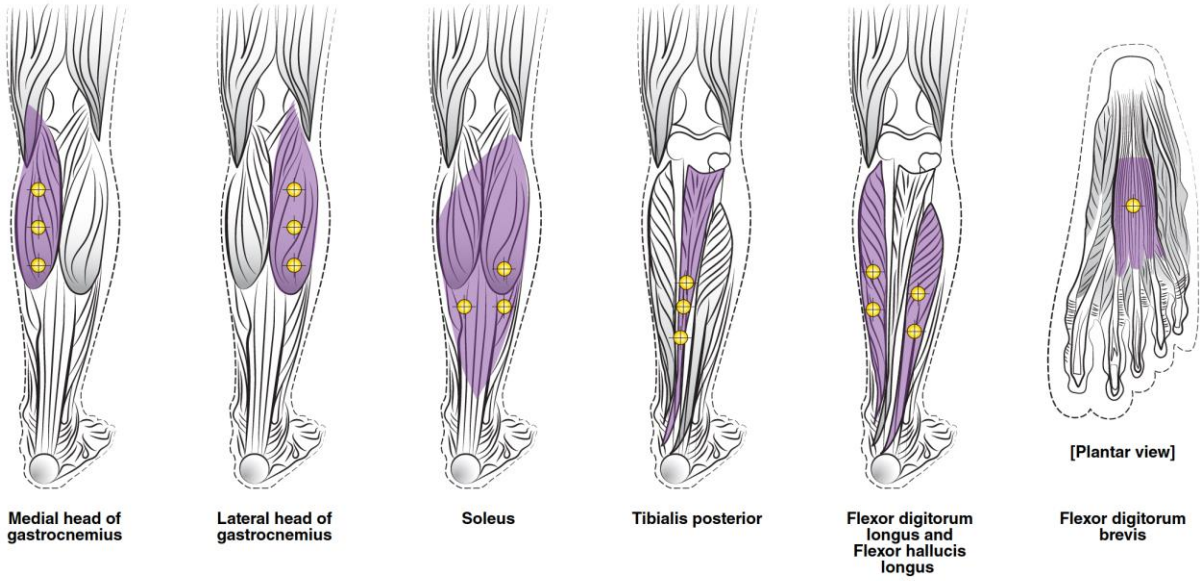
***Lower Limb:***
The recommended dose for treating adult lower limb spasticity involving the ankle and toes is 300 Units to 400 Units divided among up to 6 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, flexor digitorum longus, and flexor digitorum brevis) (see Table 4 and Figure 1 below).

If it is deemed appropriate by the treating physician, 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.

**Table 4: BOTOX® Dosing by Muscle for Adult Lower Limb Spasticity**[202]

| **Muscle** | **Recommended Dose**<br>**Total Dosage; Number of Sites** |
|---|---|
| Gastrocnemius<br>Medial head<br>Lateral head | <br>75 Units; 3 sites<br>75 Units; 3 sites |
| Soleus | 75 Units; 3 sites |
| Tibialis Posterior | 75 Units; 3 sites |
| Flexor hallucis longus | 50 Units; 2 sites |
| Flexor digitorum longus | 50 Units; 2 sites |
| Flexor digitorum brevis | 25 Units; 1 site |

**Figure 1: Injection Sites for Adult Lower Limb Spasticity**




***Equinus Foot***

For the treatment of equinus foot deformity due to spasticity in pediatric cerebral palsy, diluted BOTOX® is injected using a sterile 23 - 26 gauge needle. In clinical trials, the total dose of 4 U/kg was administered by injecting BOTOX® into each of two sites in the medial and lateral heads of the gastrocnemius muscle of the affected lower limb(s). In diplegia, the initial recommended total dose is 6 units/kg body weight divided between the affected limbs.

Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. The average duration of the therapeutic effect reported in an open-label clinical trial of 207 patients was 3.1 to 3.6 months. In this study, although the dose was 4 U/kg, the number of Units injected did not exceed 200 U.

***Primary Hyperhidrosis of the Axilla***

BOTOX® is reconstituted with 0.9% non-preserved sterile saline (100 U/4.0 mL). Using a 30 gauge needle, 50 U of BOTOX® (2.0 mL) is injected intradermally, evenly distributed in multiple sites (10-15) approximately 1-2 cm apart within the hyperhidrotic area of the axilla. The hyperhidrotic area may be defined using standard staining techniques, for example Minor's iodine-starch test.

***Chronic Migraine***

The recommended dilution is 200 U/4 mL or 100 U/2 mL, with a final concentration of 5 U per 0.1 mL (see Dilution Table 6). The recommended dose for treating chronic migraine is 155 U administered intramuscularly (IM) as 0.1 ml (5 U) injections to 31 sites using a 30-gauge, 0.5 inch needle. Injections should be divided across 7 specific head/neck muscle areas as specified in diagrams 1 – 4 and Table 5 below. A 1-inch needle may be needed in the neck region for patients with extremely 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 the minimum dose per muscle as indicated below, with half the number of injections sites administered to the left, and half to the right side of the head and neck (diagrams 1 – 4). The recommended retreatment schedule is every 12 weeks.

Diagrams 1 – 4: Recommended injection sites for chronic migraine

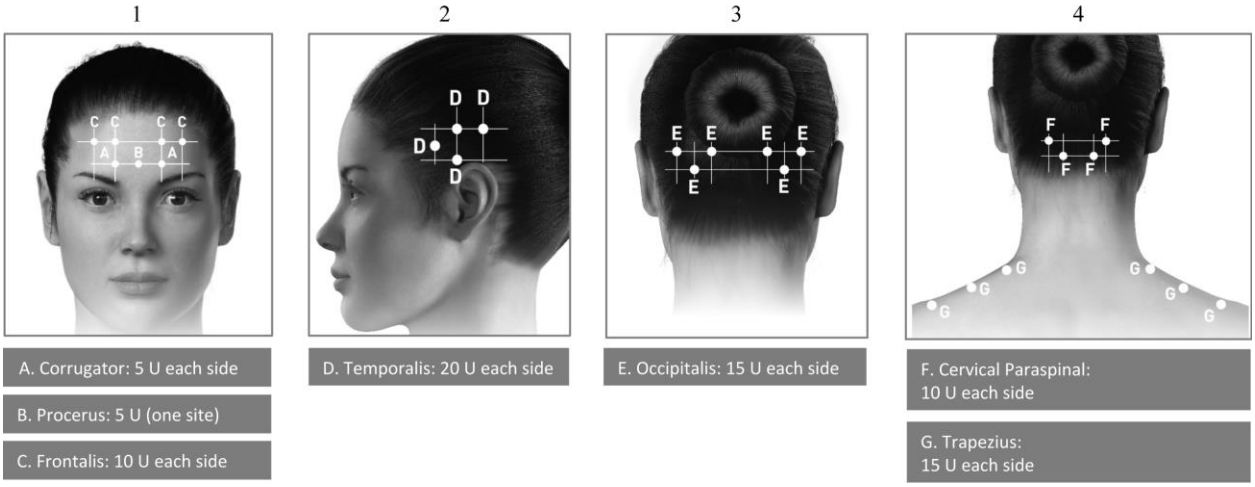


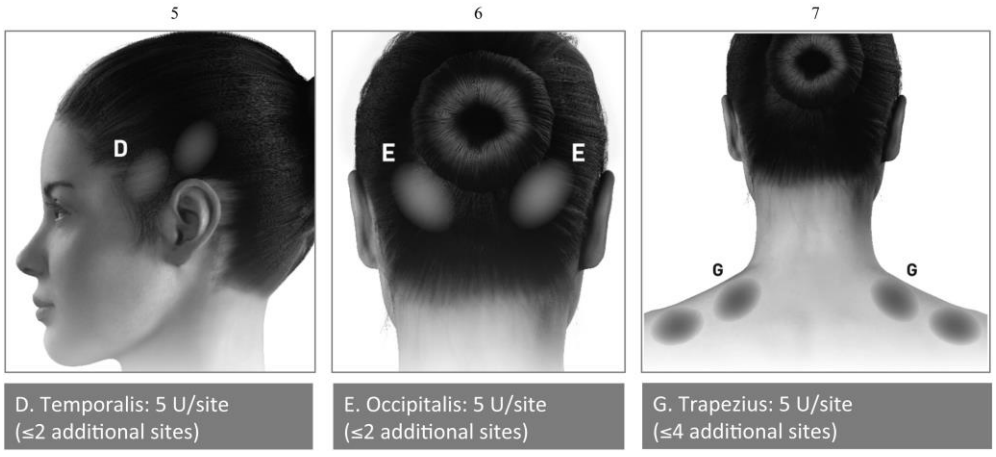
**Table 5: BOTOX® Dosing By Muscle for Chronic Migraine**

| | **Recommended Dose** |
|---|---|
| **Head/Neck Area** | **Total Number of Units (U) (number of IM injection sites[a])** |
| Corrugator[b] | 10 U (2 sites) |
| Procerus | 5 U (1 site) |
| Frontalis[b] | 20 U (4 sites) |
| Temporalis[b] | 40 U (8 sites) |
| Occipitalis[b] | 30 U (6 sites) |
| Cervical Paraspinal Muscle Group[b] | 20 U (4 sites) |
| Trapezius[b] | 30 U (6 sites) |
| **Total Dose Range:** | **155 U (31 sites)** |

[a]1IM injection site = 0.1 mL = 5 U BOTOX®
[b]Dose distributed bilaterally for minimum dose.

If there is a predominant pain location(s), optional additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in diagrams 5 – 7. This represents a total maximum dose for chronic migraine of 195 U (39 sites).

Diagrams 5 – 7: Recommended muscle groups for optional additional injections for chronic migraine




***Bladder Dysfunction***
Patients should not have urinary tract infection prior to treatment. Prophylactic antibiotics (except aminoglycosides, see DRUG INTERACTIONS) should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment.

It is recommended that patients discontinue anti-platelet therapy at least three days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

***Neurogenic Detrusor Overactivity associated with a neurological 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®.

*Reconstitution of 200 Unit Vial*
Reconstitute a 200 Unit vial of BOTOX® with 6 mL of 0.9% non-preserved 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% non-preserved 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.

*Reconstitution of 100 Unit Vial*
Reconstitute two 100 Unit vials of BOTOX®, each with 6 mL of 0.9% non-preserved 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. Complete the reconstitution by adding 6 mL of 0.9% non-preserved 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.

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

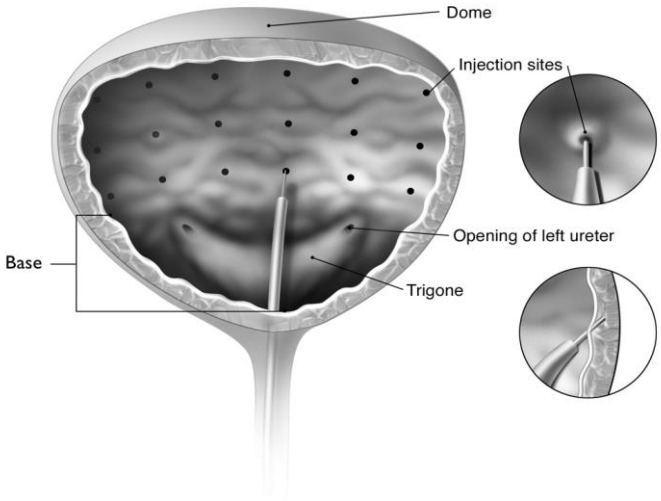
The injection needle should be filled (primed) with approximately 1 mL prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 2 below). For the final injection, approximately 1 mL of sterile normal saline should be injected so 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.

Clinical improvement may occur within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection diminished (median duration in phase 3 clinical studies was 256-295 days (36-42 weeks) for BOTOX® 200 Units), but no sooner than 3 months from the prior bladder injection. Based on patients who received treatments with only BOTOX®

200 Units from the pivotal studies through the open label extension study (N=174), the overall median duration of response was 253 days (~36 weeks).

**Figure 2 Injection Pattern for Intradetrusor Injections**




***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®. The recommended dilution is 100 Units/10 mL with 0.9% non-preserved saline solution (see Dilution Table 6). Dispose of any unused saline.

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

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

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 2 above). For the final injection, approximately 1 mL of sterile normal saline should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualization should not be drained so that patients can 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. Post void residual urine volume should be measured within 2 weeks of treatment and CIC initiated if necessary.

Clinical improvement may occur within 2 weeks. Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was 166 days [~24 weeks]), but no sooner than 3 months from the prior bladder

injection. Based on patients who received treatments with only BOTOX® 100 Units from the pivotal studies through the open label extension study (N=438), the overall median duration of response was ~212 days (~30 weeks).

***Lack of Response:***

There are several potential explanations for a lack or diminished response to an individual treatment with BOTOX®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement, patient perception of benefit compared with initial results, inappropriate storage or reconstitution, as well as neutralizing antibodies to botulinum toxin. A neutralizing antibody is defined as an antibody that inactivates the biological activity of the toxin. However, there have been patients who continued to respond to therapy and demonstrated presence of neutralizing antibodies; the proportion of patients which lose their response to botulinum toxin therapy and have demonstrable levels of neutralizing antibodies is small.

The critical factors for neutralizing antibody production are the frequency and dose of injection. Some cervical dystonia patients acquired immunity to botulinum toxin when injected at two to three week intervals with doses exceeding 300 units in a 30 day period. Some tolerance may be observed when BOTOX® is used in treating blepharospasm if treatments are given more frequently than every three months. To reduce the potential for neutralizing antibody formation, it is recommended that injection intervals should be no more frequent than two months. In general, the dose should not exceed 360 U in any three month period. For the treatment of blepharospasm, the cumulative dose of BOTOX® in a two month period should not exceed 200U. No patients among 496 chronic migraine patients with analyzed specimens showed the presence of neutralizing antibodies.

A suggested course of action when patients do not respond to BOTOX® injections is:

1) wait the usual treatment interval;
2) consider reasons for lack of response listed above;
3) more than one treatment course should be considered before classification of a patient as a non-responder;
4) test patient serum for neutralizing antibody presence.

**Missed Dose**

Missed doses may be administered as soon as is practical.

**General Administration**

An injection of BOTOX® is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see Dilution Table 6, below) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe may be attached to the electromyographic injection needle, preferably a 1.5 inch, 27 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new

sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX®.

**General Reconstitution:**
**Parenteral Products:**
To reconstitute vacuum-dried BOTOX®, use sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX® is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX® should be administered within twenty-four hours after reconstitution.

During this time period, reconstituted BOTOX® should be stored in a refrigerator (2° to 8° C). Reconstituted BOTOX® should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

**Table 6: Dilution**

| Quantity of Diluent Added (0.9% Sodium Chloride Injection) | Resulting dose Units per 0.1 mL | | |
|---|---|---|---|
| | 50 U Vial | 100 U Vial | 200 U Vial |
| 1.0 mL | 5.0 U | 10.0 U | 20.0 U |
| 2.0 mL | 2.5 U | 5.0 U | 10.0 U |
| 4.0 mL | 1.25 U | 2.5 U | 5.0 U |
| 8.0 mL | - | 1.25 U | 2.5 U |
| 10.0 mL | - | 1 U | 2 U |

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

For reconstitution technique for intradetrusor injections for neurogenic detrusor overactivity please refer to **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment,** *Neurogenic Detrusor Overactivity*.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of overdosage or injection error, additional information may be obtained by contacting Allergan Inc. at (800) 433-8871.

Overdose of BOTOX® is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are not apparent immediately post-injection. Excessive doses may produce local, or distant, generalized and profound neuromuscular paralysis. Should accidental injection or oral ingestion occur, or overdose be suspected, the person should be medically monitored for up to several weeks for progressive signs or symptoms of muscular weakness, which could be local or distant from the site of injection that may include ptosis, diplopia, swallowing and speech disorders, generalized weakness or respiratory failure. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

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

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

BOTOX® (onabotulinumtoxinA for injection) is a sterile, vacuum-dried form of purified botulinum neurotoxin type A complex, produced from a culture of the Hall strain of *Clostridium botulinum* grown in a medium containing N-Z amine, glucose and yeast extract. It is purified to a crystalline complex consisting of the neurotoxin, a non-toxic protein and four major hemagglutinin proteins.

BOTOX® blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTOX® produces partial chemical denervation of the muscle resulting in localized muscle paralysis. When chemically denervated, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus reversing muscle weakness produced by localized injection of BOTOX®. In sensory neurons, BOTOX® inhibits the release of sensory neurotransmitters (e.g., Substance P, CGRP) and downregulates the expression of cell surface receptors (e.g., TRPV1). BOTOX® also prevents and reverses sensitization in nociceptive sensory neurons.

Following intradetrusor injections, BOTOX® affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition, BOTOX® inhibits afferent neurotransmitters and sensory pathways.

The primary release procedure for BOTOX® uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's product BOTOX®. One Allergan Unit (U) of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols, Units of biological activity of BOTOX® can not be compared to or

converted into units of any other botulinum toxin activity. The specific activity of BOTOX® is approximately 20 Units/nanogram of neurotoxin protein complex.

**Pharmacodynamics**

When injected into neck muscles, BOTOX® reduces both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements include reduced angle of head turning, reduced shoulder elevation, decreased size and strength of hypertrophic muscles, and decreased pain. Based on the results of well-controlled studies, 40-58% of patients with cervical dystonia would be expected to have a significant improvement in their symptoms.

The paralytic effect on muscles injected with BOTOX® reduces the excessive, abnormal contractions of blepharospasm associated with dystonia.

When used for the treatment of strabismus, it has been postulated that the administration of BOTOX® affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the antagonist muscle.

Following injection of BOTOX® some distant muscles have shown increased electrophysiologic neuromuscular jitter. This effect is not associated with other types of electrophysiologic abnormalities, or with clinical signs of weakness or symptoms regarding either safety or efficacy.

In the treatment of pediatric cerebral palsy patients with dynamic equinus foot deformity due to spasticity, BOTOX® injections into the gastrocnemius produce an improvement in ankle position (reduction in equinus) and an improvement in gait pattern due to increased heel-to-floor contact.

In the treatment of hyperhidrosis of the axilla (N=320), BOTOX®-treated patients demonstrated a responder rate based on gravimetric assessment of 95% at week 1 and 82% at week 16. The mean percentage reduction in sweat production in the BOTOX®-treated patients ranged from 83% at week 1 to 69% at week 16. Treatment response has been reported to persist for 4 to 7 months (average of 5.2 months) in patients (N=12) treated with 50 U per axilla. Repeat injections should be administered when effects from previous injections subside.

When used for the treatment of focal spasticity BOTOX® injected into upper limb muscles reduces the objective signs and subjective symptoms of spasticity. Improvements include reduction of muscle tone, increase in range of motion, and in some patients reduction of spasticity-related disability.

When used for the prophylaxis of headaches in adults with chronic migraine BOTOX® may act as an inhibitor of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical studies.

**Pharmacokinetics**

It is believed that little systemic distribution of therapeutic doses of BOTOX® occurs. BOTOX® is not expected to be presented in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin

administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, clinical studies using single fiber electromyographic techniques have shown subtle electrophysiologic findings consistent with neuromuscular inhibition (i.e. "jitter") in muscles distant to the injection site, but these were unaccompanied by any clinical signs or symptoms of neuromuscular inhibition from the effects of botulinum toxin.

## STORAGE AND STABILITY

- Store the vacuum-dried product either in a refrigerator at 2º - 8ºC, or in a freezer at or below -5º C.
- Administer BOTOX® within 24 hours after the vial is removed from the freezer and reconstituted in the vial.
- During these 24 hours, BOTOX® reconstituted in the vial should be stored in a refrigerator (2º to 8º C).
- Reconstituted BOTOX® should be clear, colorless and free of particulate matter.
- If reconstituted BOTOX® is further diluted in a syringe for intradetrusor injections, it should be used immediately.
- Do not freeze reconstituted BOTOX®.
- At the time of use, product acceptability should be confirmed relative to the expiration date indicated on the product vial and outer box.

## SPECIAL HANDLING INSTRUCTIONS

All vials, including expired vials, or equipment used in direct contact with the drug should be disposed of medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of dilute hypochlorite solution (0.5% or 1%) for five minutes is recommended prior to disposal as medical waste.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

BOTOX® is available in 50, 100 and 200 unit (U) sterile vials of *Clostridium botulinum* toxin type A in a vacuum-dried form without a preservative. One Allergan unit (U) corresponds to the calculated median lethal dose ($LD_{50}$) in mice using reconstituted BOTOX® and injected intraperitoneally.

The quantities of the ingredients in each vial are listed below:

| **INGREDIENTS** | **50 Allergan U Vial** | **100 Allergan U Vial** | **200 Allergan U Vial** |
|---|---|---|---|
| *Clostridium botulinum* toxin type A neurotoxin complex (900kD) | 50 U | 100 U | 200 U |
| Human Serum Albumin | 0.25 mg | 0.5 mg | 1.0 mg |
| Sodium Chloride | 0.45 mg | 0.9 mg | 1.8 mg |

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

Proper name: OnabotulinumtoxinA for injection

Molecular formula: The amino acid composition of the neurotoxin complex (based on the average of three independent assays) is as follows: $Asx_{1442}Thr_{485}Ser_{531}Glx_{719}Pro_{237}Gly_{395}Ala_{341}Val_{390}Cys_{103}Met_{84}Ile_{644}Leu_{718}Tyr_{499}Phe_{356}Lys_{486}His_{47}Arg_{241}Trp_{115}$ where Asx represents a mixture of Asn and Asp, and Glx represents a mixture of Gln and Glu.

Molecular mass: 900kD

Structural formula: The Purified Neurotoxin Complex is a 900 kD complex composed of a 150 kD neurotoxin, a 130 kD non-toxic, non-hemagglutinating protein, and various hemagglutinins ranging between 14 and 48 kD. The 150 kD neurotoxin is produced as a single-chain polypeptide. The polypeptide is activated by the proteolytic enzymes of *C. botulinum* during fermentation in a process known as nicking, which converts the single-chain polypeptide into a di-chain polypeptide comprised of a 97 kD heavy chain linked by a disulfide bond to a 53 kD light chain. The complete amino acid sequence of the neurotoxin was derived from a cloned DNA sequence. The neurotoxin, before nicking, consists of 1296 amino acids (1295 after the Met at the N-terminus is cleaved. Ten amino acid residues, from $Leu_{438}$ - $Lys_{447}$, are removed during nicking.

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

## CLINICAL TRIALS

***Blepharospasm***

The paralytic effect on muscles injected with BOTOX® reduces the excessive, abnormal contractions of blepharospasm associated with dystonia.

In one study, injection of botulinum toxin was evaluated in 27 patients with essential blepharospasm. Twenty-six (26) of the patients had previously undergone drug treatment utilizing benztropine mesylate, clonazepam and/or baclofen without adequate clinical results. Three of these patients then underwent muscle stripping surgery, again without an adequate

outcome. One patient of the 27 was previously untreated. Twenty-five (25) of the 27 patients reported improvement within 48 hours following injection of botulinum toxin. Blepharospasm in one of the other patients was later controlled with a higher dosage of botulinum toxin. The remaining patient reported only mild improvement but remained functionally impaired.

In a double-blind, placebo-controlled study, 12 patients with blepharospasm were evaluated; 8 patients received botulinum toxin and 4 received placebo. All patients who received botulinum toxin improved compared to none in the placebo group. Among the botulinum toxin-treated patients, the mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The mean duration of treatment effects was 12.5 weeks.

In an open trial, 1684 patients with blepharospasm showed clinical improvement after treatment with BOTOX® lasting an average of 12.5 weeks prior to the need for re-treatment.

***Strabismus***

When used for the treatment of strabismus, it has been postulated that the administration of BOTOX® affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the antagonist muscle.

In an open trial, 677 patients with strabismus were treated with one or more injections of BOTOX®. Fifty-five percent (55%) of these patients were improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection. These results are consistent with results from additional open label trials which were conducted for this indication.

***Cervical dystonia (spasmodic torticollis)***

When injected into neck muscles, BOTOX® (onabotulinumtoxinA for injection) reduces both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements include reduced angle of head turning, reduced shoulder elevation, decreased size and strength of hypertrophic muscles, and decreased pain. Based on the results of well-controlled studies, 40-58% of patients with cervical dystonia would be expected to have a significant improvement in their symptoms.

In a double-blind, vehicle-controlled parallel study, 51 patients with idiopathic cervical dystonia (spasmodic torticollis) were evaluated. Patients treated with BOTOX® experienced an average of 8 to 12 degrees decrease in head rotation at rest, corresponding to a mean decrease of 13% to 20%, respectively. There was also a significant decrease in strength and size of the contralateral sternocleidomastoid and trapezii (i.e., muscles involved in head rotation). Vehicle-treated patients showed a mean decrease of only 0 to 4 degrees (0% to 6%) of head rotation at rest, and had no change in muscle strength or size. The difference in head rotation between treatment groups was statistically significant. Among BOTOX® treated patients, improvement was reported by 42%, 58% and 57% of the patients at 2, 6 and 12 weeks after injection, respectively. Improvement was reported by 8%, 8% and 17% of vehicle-treated subjects at the same time points, respectively.

In a double-blind, vehicle-controlled crossover study, there was a significant decrease in the size of the sternocleidomastoid muscle contralateral to head turning following BOTOX® compared to

placebo injection. By crossover analysis, 41% of patients reported a positive global assessment of response after BOTOX® injection (which includes measures of head rotation, head tilt, anterocollis, retrocollis, duration of sustained movements, shoulder elevation and tremor duration and severity), compared to 14% after vehicle injection.

Two additional double-blind, vehicle-controlled crossover studies evaluated the efficacy of BOTOX® in patients with cervical dystonia. There was a significant decrease in discomfort in the patients treated with BOTOX® in one study. In the other study, patients treated with BOTOX® had a mean decrease in head rotation of 18% (crossover analysis) and 30% (parallel analysis) compared with a mean decrease in head rotation of 3% (crossover) and 16% (parallel) in patients treated with placebo. In both of these studies, the global assessment of cervical dystonia showed trends of improvement for patients treated with BOTOX® relative to those treated with vehicle.

***Focal Spasticity***

***Upper Limb:***

The efficacy of BOTOX® used for the treatment of upper limb spasticity associated with stroke was evaluated in double-blind and open label studies in 387 unique patients who received 531 treatment exposures.

In a three month, double-blind, placebo controlled study, 126 patients with upper limb spasticity post-stroke were treated with 200 U to 240 U of BOTOX® into the wrist, finger, and thumb flexor muscles. A clinically significant greater reduction in muscle tone was observed in BOTOX® treated patients compared to placebo as measured on the Ashworth scale 1 to 12 weeks post-treatment. The Physician Global Assessment showed parallel statistically significant improvements. Furthermore, patients treated with BOTOX® had significant improvement for a pre-determined, targeted disability item associated with upper limb spasticity at 4 to 12 weeks post-treatment.

In three- and four-month, double-blind, placebo-controlled, dose-ranging studies involving a total of 130 patients with upper limb spasticity post-stroke, patients were treated with a total dose of up to 300 U or 360 U of BOTOX®. Improvements in wrist, elbow and finger flexor muscle tone were reported at the highest dose in each study at various timepoints. The Physician Global Assessment also showed significant benefit at doses ranging from 75 to 360 units at various timepoints.

***Lower Limb:***

The efficacy and safety of BOTOX® for the treatment of lower limb spasticity was evaluated in a randomized, multi-center, double-blind, placebo-controlled study. This study included 468 post-stroke patients (233 BOTOX® and 235 placebo) wth ankle spasticity (Modified Ashworth Scale [MAS] ankle score of at least 3) who were at least 3 months post-stroke. BOTOX® 300 to 400 Units or placebo were injected intramuscularly into the study mandatory muscles gastrocnemius, soleus, and tibialis posterior and optional muscles including flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris. The use of electromyographic guidance, nerve stimulation, or ultrasound was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

The primary endpoint was the average change from baseline of weeks 4 and 6 MAS ankle score and a key secondary endpoint was the average CGI (Physician Global Assessment of Response) at weeks 4 and 6. The MAS uses a similar scoring system as the Ashworth Scale. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement.

**Table 7: Primary and Key Secondary Efficacy Endpoints**

| | **BOTOX® 300 to 400 Units (ITT) (N=233)** | **Placebo (N=235)** | **P-value[1&2] Difference 95% CI** |
|---|---|---|---|
| LS Mean Changes from Baseline in Ankle Plantar Flexors in MAS Score Week 4 and 6 Average | -0.81 | -0.61 | 0.010<br>-0.2<br>(−0.356, −0.050) |
| LS Mean Clinical Global Impression Score by Investigator Week 4 and 6 Average | 0.86 | 0.65 | 0.012<br>0.22<br>(0.048, 0.383) |

[1]P-values and 95% CIs for between-group comparisons were obtained from an ANCOVA model including treatment and center as factors, with baseline ankle MAS-B and muscle group injected as covariates. Estimated differences were based on the LS means.

[2] To control the type 1 error rate for multiple secondary endpoints, a gatekeeping approach was used. The first secondary endpoint (CGI) could only indicate significance if the primary endpoint (MAS-B) was significant.

***Equinus foot***

In a three-month, double-blind, placebo-controlled, parallel study, 145 ambulatory children with cerebral palsy, 2 to 16 years of age, were evaluated. Patients exhibited muscle spasticity of the lower extremity(ies) associated with an equinovalgus foot position during gait. A significantly greater number of patients treated with BOTOX® vs. placebo demonstrated improvement based on a physician's rating of dynamic gait which was composed of assessments of gait pattern, ankle position, hindfoot position during foot strike, knee position during gait, degree of crouch and speed of gait. Improvement was reported by 53%, 50%, 60% and 54% of BOTOX®-treated patients vs. 25%, 27%, 25% and 32% of placebo-treated patients at Weeks 2, 4, 8 and 12, respectively. Of the individual assessments which were included in the physician's rating of dynamic gait, a significantly greater number of BOTOX®-treated vs. placebo-treated subjects had improvements in gait pattern (Weeks 2, 8, and 12) and ankle position (Weeks 2, 4, 8 and 12).

Electromyography confirmed that BOTOX® produces a partial denervation of the gastrocnemius muscle. No significant changes in electromyography were seen in the placebo-treated patients.

In a long-term, open-label study, 207 patients were evaluated for up to three years. The percent of patients who showed an improvement based on the physician's rating of dynamic gait ranged from 41% to 67% over the three-year period. Of the individual assessments which were included in the physician's rating of dynamic gait, significant improvements in gait pattern were seen at every visit over the three-year period.

***Primary Hyperhidrosis of the Axillae***

When injected intradermally, BOTOX® produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating. The efficacy and safety of BOTOX® for the treatment of primary axillary hyperhidrosis were evaluated in a randomized, multi-center, double-blind, placebo-controlled study.

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

***Chronic migraine***

BOTOX® was evaluated in two multi-national, multi-center 56 week studies that included a 24 week, 2 injection cycle, double-blind phase comparing BOTOX® to placebo that was followed by a 32-week, 3 injection cycle, open-label phase. A total of 1,384 chronic migraine adults who had either never received or were not using any concurrent headache prophylaxis, had > 15 headache days, with 50% being migraine/probable migraine, and > 4 headache episodes during a 28-day baseline phase were studied in 2 phase 3 clinical trials. These patients were randomized to placebo or to 155 U - 195 U BOTOX® injections every 12 weeks, maximum 5 injection cycles. Patients were allowed to use acute headache treatments (65.5% overused acute treatments during the baseline period). The number (percentage) of patients who received BOTOX® injections at 31 sites and at 39 sites at Week 12 were N=345/627 (55.0%) and N=44/627 (7.0%), respectively.

**Table 8: Phase 3 Study 1*: Least Square (LS) Mean Change from Baseline, Between-Group Differences and 99% Confidence Intervals for Primary and Secondary Efficacy Variables at Week 24 Primary Timepoint**

| **Efficacy per 28 days[c]** | **BOTOX® (N=341)** | **Placebo (N=338)** | **Between-Group Difference (99% CI)[a]** | **P-value [a,b]** |
|---|---|---|---|---|
| Frequency of headache days | -7.8 | -6.4 | -1.4 (-2.72, -0.09) | 0.006 |
| Frequency of migraine/probable migraine episodes | -5.0 | -4.5 | -0.5 (-1.45, 0.50) | 0.206 |
| Frequency of migraine/probable migraine days | -7.6 | -6.0 | -1.6 (-2.91, -0.27) | 0.002 |
| Frequency of headache episodes[d] | -5.4 | -5.0 | -0.4 (-1.36, 0.63) | 0.344 |
| Frequency of acute headache pain medication intakes | -10.1 | -9.8 | -0.3 (-3.82, 3.12) | 0.795 |

* Allergan study 191622-079

[a] To control the type-1 error rate at 0.05, p-values were examined relative to 0.01 under a Bonferroni multiple-comparison adjustment for the 5 variables that were protocol-specified as primary or secondary. Accordingly, for the least-squares means' difference between treatment groups, 99% confidence intervals are displayed rather than 95% confidence intervals.

[b] P-values for between-treatment comparisons are from covariate analysis of variance (ANCOVA), with baseline values as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata, where the type III sum of squares was used.

[c] Missing values were estimated using modified last observation carried forward, with the patient's most-recent previous score multiplied by the change rate across non-missing observations for all other patients, applied iteratively across sequential time periods.

[d] Primary endpoint

**Table 9: Phase 3 Study 2*: LS Mean Change from Baseline, Between-Group Differences and 95% Confidence Intervals for Primary and Secondary Efficacy Variables at Week 24 Primary Timepoint**

| Efficacy per 28 days[c] | BOTOX® (N=347) | Placebo (N=358) | Between-Group Difference (95% CI) | P-value[a,b] |
|---|---|---|---|---|
| Frequency of headache days[e] | -9.2 | -6.9 | -2.3 (-3.25, -1.31) | <0.001 |
| Frequency of migraine/probable migraine days | -8.8 | -6.5 | -2.3 (-3.31, -1.36) | <0.001 |
| Number of moderate/severe headache days | -8.4 | -6.0 | -2.4 (-3.37, -1.48) | <0.001 |
| Total cumulative hours of headache on headache days | -134.15 | -94.54 | -39.6 (-58.23, -21.05) | <0.001 |
| Proportion of patients with severe (≥60) Headache Impact Test (HIT)-6 score[d] | 66.3% | 76.5% | -10.3% (-16.9, -3.6) | 0.003 |
| Frequency of headache episodes | -5.6 | -4.6 | -1.0 (-1.65, -0.33) | 0.003 |

* Allergan study 191622-080

[a] To control the type 1 error rate for multiple secondary endpoints, a gatekeeping approach was used for the five secondary variables at the primary visit (week 24). Each secondary variable could only indicate significance if the primary variable and each secondary variable ranked ahead of it indicated statistical significance.

[b] P-values for between-treatment comparisons are from covariate analysis of variance (ANCOVA), with baseline values as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata, where the type III sum of squares was used.

[c] Missing values were estimated using modified last observation carried forward, with the patient's most-recent previous score multiplied by the change rate across non-missing observations for all other patients, applied iteratively across sequential time periods.

[d] P-values from statistical comparisons are for raw values, not for changes from baseline.

[e] Primary endpoint

In Study 1, at the Week 24 primary timepoint, the mean changes from baseline in total cumulative hours of headache on headache days were -106.7 hours in the BOTOX® group and -70.4 hours in the placebo group. At the Week 24 primary timepoint, the mean changes from baseline for total HIT-6 score were -4.7 in the BOTOX® group and -2.4 in the placebo group in Study 1, and -4.9 in the BOTOX® group and -2.4 in the placebo group in Study 2.

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

BOTOX® for chronic migraine has not been evaluated in clinical trials beyond 5 injection cycles.

***Neurogenic Detrusor Overactivity associated with a neurologic condition***

Two double-blind, placebo-controlled, randomized, multi-center Phase 3 clinical studies were conducted in patients with urinary incontinence due to neurogenic detrusor overactivity who were either spontaneously voiding or using catheterization. A total of 691 spinal cord injury or multiple sclerosis patients, not adequately managed with at least one anticholinergic agent, 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 phase 3 studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX® (200 Units and 300 Units) at the primary efficacy time point at week 6. Significant improvements in urodynamic parameters including increase in maximum cystometric capacity and decreases in peak detrusor pressure during the first involuntary detrusor contraction were observed. These primary and secondary endpoints are shown in Tables 10 and 11, and Figures 3 and 4.

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

**Table 10: Primary and Secondary Endpoints at Baseline and Change from Baseline in Study 1 (ITT population with LOCF Imputation)**

| | **BOTOX® 200 Units (N=135)** | **Placebo (N=149)** | **Treatment difference*** | **p-values** |
|---|---|---|---|---|
| **Weekly Frequency of Urinary Incontinence*** | | | | |
| N | 135 | 149 | | |
| Mean Baseline | 32.3 | 28.3 | | |
| Mean Change at Week 2 | -15.3 | -10.0 | -5.3 | |
| **Mean Change at Week 6[a]** | **-19.9** | **-10.6** | **-9.3** (-13.2, -5.4) | **p<0.001** |
| Mean Change at Week 12 | -19.8 | -8.8 | -11.0 | |
| **Maximum Cystometric Capacity (mL)** | | | | |
| N | 123 | 129 | | |
| Mean Baseline | 253.8 | 259.1 | | |
| **Mean Change at Week 6[b]** | **+135.9** | **+12.1** | **123.9** (89.1, 158.7) | **p<0.001** |

| | BOTOX® 200 Units (N=135) | Placebo (N=149) | Treatment difference* | p-values |
|---|---|---|---|---|
| **Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction ($cmH_20$)** | | | | |
| N | 41 | 103 | | |
| Mean Baseline | 63.1 | 57.4 | | |
| **Mean Change at Week 6[b]** | **-28.1** | **-3.7** | -24.4 | |

* Mean change, treatment difference and p-value are based on a LOCF analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.
[a] Primary endpoint
[b] Key secondary endpoints

*Study 1 = Study* 191622-515
*Study 2 = Study* 191622-516

**Table 11: Primary and Secondary Endpoints at Baseline and Change from Baseline in Study 2 (ITT population with LOCF Imputation)**

| | BOTOX® 200 Units (N=92) | Placebo (N=92) | Treatment difference* | p-values |
|---|---|---|---|---|
| **Weekly Frequency of Urinary Incontinence*** | | | | |
| N | 92 | 92 | | |
| Mean Baseline | 32.5 | 36.7 | | |
| Mean Change at Week 2 | -18.1 | -7.9 | -10.3 | |
| **Mean Change at Week 6[a]** | **-19.8** | **-10.8** | **-9.0** (-14.8, -3.3) | **p=0.002** |
| Mean Change at Week 12 | -19.6 | -10.7 | -8.9 | |
| **Maximum Cystometric Capacity (mL)** | | | | |
| N | 88 | 85 | | |
| Mean Baseline | 239.6 | 253.8 | | |
| **Mean Change at Week 6[b]** | **+150.8** | **+2.8** | **148.0** (101.8, 194.3) | **p<0.001** |
| **Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction ($cmH_20$)** | | | | |
| N | 29 | 68 | | |
| Mean Baseline | 65.6 | 43.7 | | |
| **Mean Change at Week 6[b]** | **-28.7** | **+2.1** | **-30.7** | |

* Mean change, treatment difference and p-value are based on a LOCF analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors.
[a] Primary endpoint
[b] Key secondary endpoints

*Study 1 = Study* 191622-515
*Study 2 = Study* 191622-516

**Figure 3: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 1**

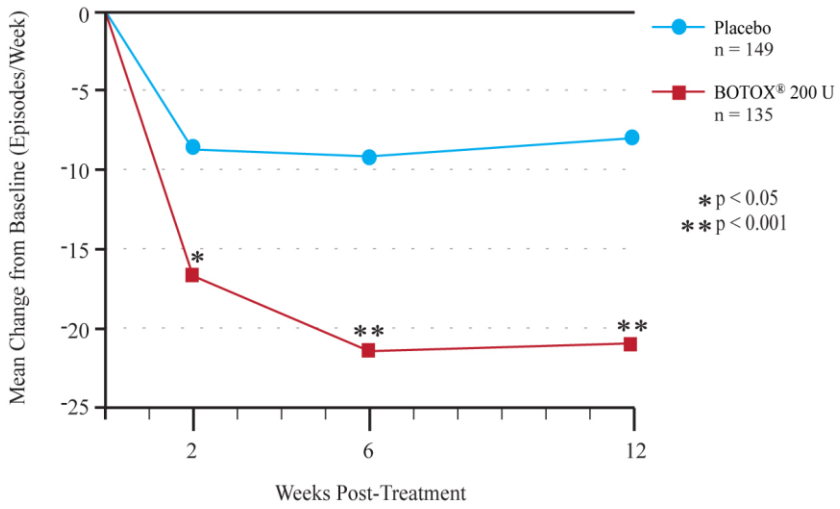
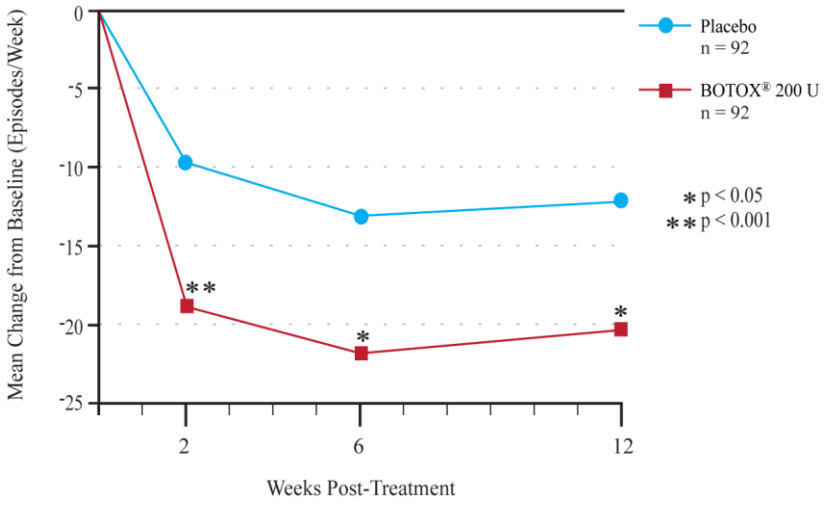



**Figure 4: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 2**




The median duration of response in the two pivotal studies, based on patient request for re-treatment, was 256-295 days (36-42 weeks) for the 200 Unit dose group compared to 92 days (13 weeks) with placebo. Retreatment criteria were: patient request, at least 12 weeks since previous treatment, and < 50% reduction (Study 1) or < 30% reduction (Study 2) from baseline in urinary incontinence episodes. The median duration of response in patients who continued into the open label extension study and received treatments with only BOTOX® 200 Units (N=174) was 253 days (~36 weeks).

A total of 397 patients were evaluated in a long term extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments.

In the pivotal studies, none of the 475 neurogenic detrusor overactivity patients with analyzed specimens developed the presence of neutralizing antibodies. In patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX® 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Four of these eight patients continued to experience clinical benefit.

***Post-Approval Commitment Study***

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

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX® (100 Units) at the primary efficacy time point at week 6.

**Table 12: Study Baseline and Mean Change from Baseline in Primary Endpoints (Daily Average Frequency of Urinary Incontinence Episodes) and Mean Changes from Baseline for Secondary Endpoints (ITT population with LOCF)**

| | **BOTOX 100 Units (N=66)** | **Placebo (N=78)** | **P-value LS mean difference 95% CI** |
|---|---|---|---|
| Daily Average Frequency of Urinary Incontinence Episodes | | | |
| Mean (Baseline) | 4.18 | 4.32 | |
| Mean (Week 6) | -3.34 | -1.10 | P<0.001 |
| LS mean (Week 6) | -3.39 | -1.07 | -2.32 (-2.97, -1.66) |
| Maximum Cystometic Capacity (mL) | N=62 | N=72 | |
| Mean (Week 6) | +127.2 | -1.8 | |
| Min, Max (Week 6) | -139, +449 | -239, +221 | |
| Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cm $H_2O$) | N=25 | N=51 | |
| Mean (Week 6) | -19.6 | +3.7 | |
| Min, Max (Week 6) | -170, +27 | -85, +87 | |

*LS = least squares

*LS means, the between-group difference of LS means, its p-value and its 95% CI are based on an ANCOVA model with treatment group and propensity score stratification as factors, and baseline value as a covariate.

***Overactive Bladder***
Two double-blind, placebo-controlled, randomized, multi-center, 24-week Phase 3 clinical studies were conducted in patients with OAB with symptoms of urinary incontinence, urgency, and frequency. 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).

In both studies, significant improvements compared to placebo in the change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX® (100 U) at the primary time point of week 12, including the proportion of dry patients. Using the Treatment Benefit Scale, the proportion of patients reporting a positive treatment response (their condition has been 'greatly improved' or 'improved') was significantly greater in the BOTOX® group compared to the placebo group in both studies. Significant improvements compared to placebo were also observed for the daily frequency of micturition, urgency, and nocturia episodes. Volume voided per micturition was also significantly higher. Significant improvements were observed in all OAB symptoms from week 2.

BOTOX® treatment was associated with significant improvements over placebo in health-related quality of life as measured by the Incontinence Quality of Life (I-QOL) questionnaire (including avoidance and limiting behavior, psychosocial impact, and social embarrassment) and the King's Health Questionnaire (KHQ) (including incontinence impact, role limitations, social limitations, physical limitations, personal relationships, emotions, sleep/energy, and severity/coping measures).

A total of 834 patients were evaluated in a long term extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments.

The median duration of response following BOTOX® treatment, based on patient request for re-treatment, was 166 days (~24 weeks). Retreatment criteria for all phase 3 studies were: patient request, at least 12 weeks since previous treatment, and at least 2 urinary incontinence episodes in 3 days. The median duration of response in patients who continued into the open label extension study and received treatments with only BOTOX® 100 Units (N=438) was 212 days (~30 weeks).

In the pivotal studies, none of the 615 (0%) patients with analyzed specimens developed the presence of neutralizing antibodies. In patients with analyzed specimens from the pivotal phase 3 and the open-label extension studies, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX® 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. One of these three patients continued to experience clinical benefit.

Results from the pivotal studies are presented below:

**Table 13: Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in the Pooled Pivotal Studies**

| **Endpoint**<br>Timepoint | **BOTOX® 100 Units (N=557)** | **Placebo (N=548)** | **P-value** |
|---|---|---|---|
| **Daily Frequency of Urinary Incontinence Episodes*** | | | |
| Mean Baseline | 5.49 | 5.39 | |
| Mean Change at Week 2 | -2.85 | -1.21 | < 0.001 |
| Mean Change at Week 6 | -3.11 | -1.22 | < 0.001 |
| **Mean Change at Week 12[a]** | **-2.80** | **-0.95** | **< 0.001** |
| **Proportion with Positive Treatment Response using Treatment Benefit Scale (%)** | | | |
| Week 2 | 64.4 | 34.7 | < 0.001 |
| Week 6 | 68.1 | 32.8 | < 0.001 |
| **Week 12[a]** | **61.8** | **28.0** | **< 0.001** |
| **Daily Frequency of Micturition Episodes** | | | |
| Mean Baseline | 11.99 | 11.48 | |
| Mean Change at Week 2 | -1.53 | -0.78 | < 0.001 |
| Mean Change at Week 6 | -2.18 | -0.97 | < 0.001 |
| **Mean Change at Week 12[b]** | **-2.35** | **-0.87** | **< 0.001** |
| **Daily Frequency of Urgency Episodes** | | | |
| Mean Baseline | 8.82 | 8.31 | |
| Mean Change at Week 2 | -2.89 | -1.35 | < 0.001 |
| Mean Change at Week 6 | -3.56 | -1.40 | < 0.001 |
| **Mean Change at Week 12[b]** | **-3.30** | **-1.23** | **< 0.001** |
| **Incontinence Quality of Life Total Score** | | | |
| Mean Baseline | 34.1 | 34.7 | |
| **Mean Change at Week 12[bc]** | **+22.5** | **+6.6** | **< 0.001** |
| **King's Health Questionnaire: Role Limitation** | | | |
| Mean Baseline | 65.4 | 61.2 | |
| **Mean Change at Week 12[bc]** | **-25.4** | **-3.7** | **< 0.001** |
| **King's Health Questionnaire: Social Limitation** | | | |
| Mean Baseline | 44.8 | 42.4 | |
| **Mean Change at Week 12[bc]** | **-16.8** | **-2.5** | **< 0.001** |

* Percentage of patients who were dry (without incontinence) at week 12 was 27.1% for the BOTOX® group and 8.4% for placebo group. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 46.0% and 60.5% in the BOTOX® group compared to 17.7% and 31.0% in the placebo group, respectively.

[a] Co-primary endpoints

[b] Secondary endpoints

[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

**Table 14: Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in Study 1**

| **Endpoint**<br>Timepoint | **BOTOX® 100 Units (N=280)** | **Placebo (N=277)** | **P-value** |
|---|---|---|---|
| **Daily Frequency of Urinary Incontinence Episodes*** | | | |
| Mean Baseline | 5.47 | 5.09 | |
| Mean Change at Week 2 | -2.85 | -1.09 | < 0.001 |
| Mean Change at Week 6 | -3.05 | -1.07 | < 0.001 |
| **Mean Change at Week 12[a]** | **-2.65** | **-0.87** | **< 0.001** |
| **Proportion with Positive Treatment Response using Treatment Benefit Scale (%)** | | | |
| Week 2 | 64.5 | 32.6 | < 0.001 |
| Week 6 | 66.9 | 34.7 | < 0.001 |
| **Week 12[a]** | **60.8** | **29.2** | **< 0.001** |
| **Daily Frequency of Micturition Episodes** | | | |
| Mean Baseline | 11.98 | 11.20 | |
| Mean Change at Week 2 | -1.58 | -0.79 | 0.041 |
| Mean Change at Week 6 | -1.96 | -0.98 | < 0.001 |
| **Mean Change at Week 12[b]** | **-2.15** | **-0.91** | **< 0.001** |
| **Daily Frequency of Urgency Episodes** | | | |
| Mean Baseline | 8.54 | 7.85 | |
| Mean Change at Week 2 | -2.83 | -1.34 | < 0.001 |
| Mean Change at Week 6 | -3.21 | -1.45 | < 0.001 |
| Mean Change at Week 12[b] | -2.93 | -1.21 | < 0.001 |
| **Incontinence Quality of Life Total Score** | | | |
| Mean Baseline | 36.5 | 37.3 | |
| **Mean Change at Week 12[bc]** | **+21.9** | **+6.8** | **< 0.001** |
| **King's Health Questionnaire: Role Limitation** | | | |
| Mean Baseline | 61.2 | 56.2 | |
| **Mean Change at Week 12[bc]** | **-24.3** | **-2.4** | **< 0.001** |
| **King's Health Questionnaire: Social Limitation** | | | |
| Mean Baseline | 40.5 | 39.4 | |
| **Mean Change at Week 12[bc]** | **-17.3** | **-3.8** | **< 0.001** |

* Percentage of patients who were dry (without incontinence) at week 12 was 22.9% for the BOTOX® group and 6.5% for placebo group. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 44.6% and 57.5% in the BOTOX® group compared to 15.2% and 28.9% in the placebo group, respectively.

[a] Co-primary endpoints

[b] Secondary endpoints

[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

**Table 15: Primary and Secondary Efficacy Endpoints at Baseline and Change from Baseline in Study 2**

| **Endpoint**<br>Timepoint | **BOTOX® 100 Units (N=277)** | **Placebo (N=271)** | **P-value** |
|---|---|---|---|
| **Daily Frequency of Urinary Incontinence Episodes*** | | | |
| Mean Baseline | 5.52 | 5.70 | |
| Mean Change at Week 2 | -2.85 | -1.34 | < 0.001 |
| Mean Change at Week 6 | -3.18 | -1.37 | < 0.001 |
| **Mean Change at Week 12[a]** | **-2.95** | **-1.03** | **< 0.001** |
| **Proportion with Positive Treatment Response using Treatment Benefit Scale (%)** | | | |
| Week 2 | 64.2 | 36.8 | < 0.001 |
| Week 6 | 69.3 | 30.9 | < 0.001 |
| **Week 12[a]** | **62.8** | **26.8** | **< 0.001** |
| **Daily Frequency of Micturition Episodes** | | | |
| Mean Baseline | 12.01 | 11.77 | |
| Mean Change at Week 2 | -1.48 | -0.77 | 0.009 |
| Mean Change at Week 6 | -2.40 | -0.97 | < 0.001 |
| **Mean Change at Week 12[b]** | **-2.56** | **-0.83** | **< 0.001** |
| **Daily Frequency of Urgency Episodes** | | | |
| Mean Baseline | 9.11 | 8.78 | |
| Mean Change at Week 2 | -2.95 | -1.36 | < 0.001 |
| Mean Change at Week 6 | -3.91 | -1.35 | < 0.001 |
| **Mean Change at Week 12[b]** | **-3.67** | **-1.24** | **< 0.001** |
| **Incontinence Quality of Life Total Score** | | | |
| Mean Baseline | 31.7 | 32.1 | |
| **Mean Change at Week 12[bc]** | **+23.1** | **+6.3** | **< 0.001** |
| **King's Health Questionnaire: Role Limitation** | | | |
| Mean Baseline | 69.6 | 66.4 | |
| **Mean Change at Week 12[bc]** | **-26.5** | **-5.0** | **< 0.001** |
| **King's Health Questionnaire: Social Limitation** | | | |
| Mean Baseline | 49.1 | 45.4 | |
| **Mean Change at Week 12[bc]** | **-16.2** | **-1.3** | **< 0.001** |

* Percentage of patients who were dry (without incontinence) at week 12 was 31.4% for the BOTOX® group and 10.3% for placebo group. The proportions achieving at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 47.3% and 63.5% in the BOTOX® group compared to 20.3% and 33.2% in the placebo group, respectively.

[a] Co-primary endpoints

[b] Secondary endpoints

[c] Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

**Figure 5: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Pooled Pivotal Studies**

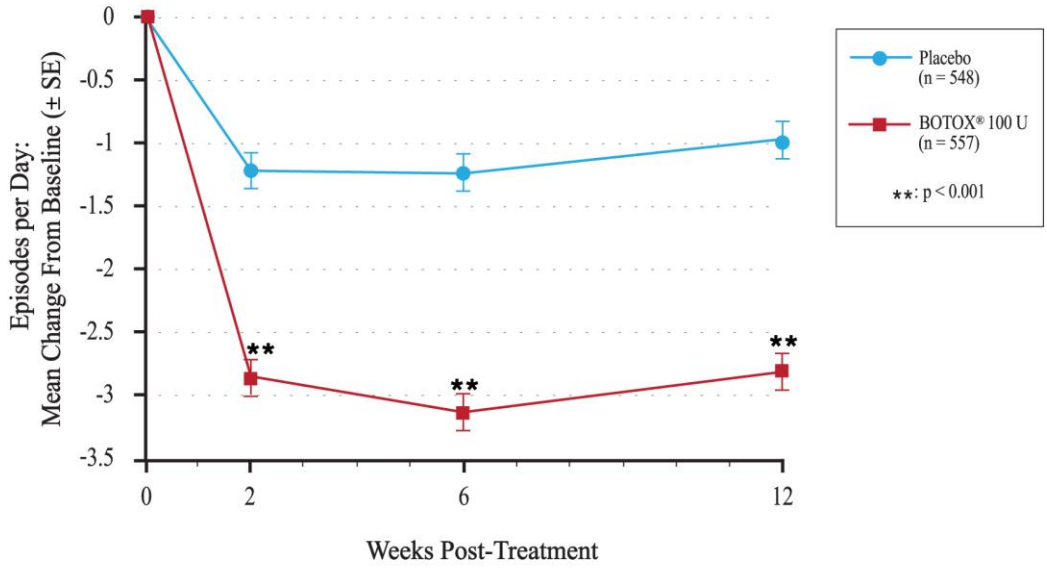



**Figure 6: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 1**

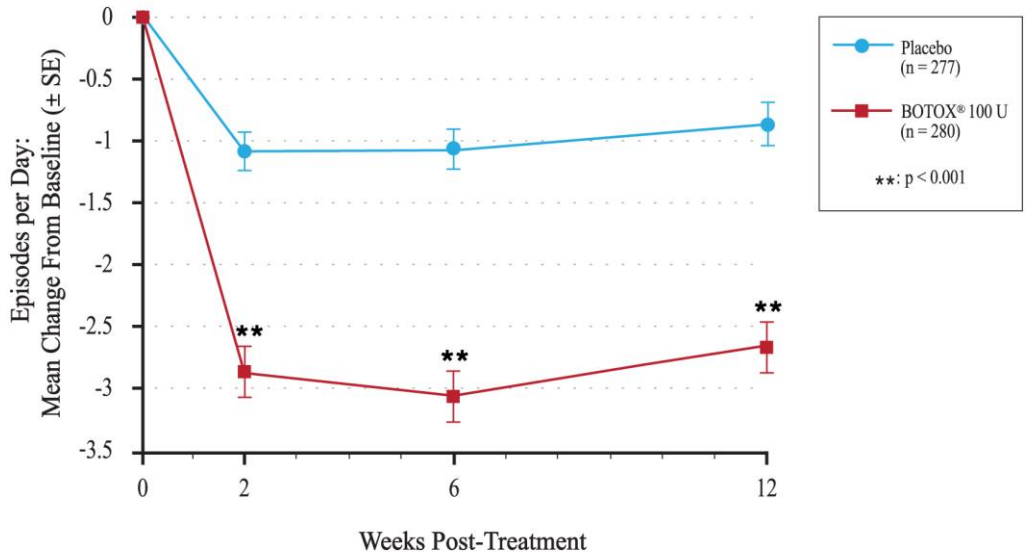
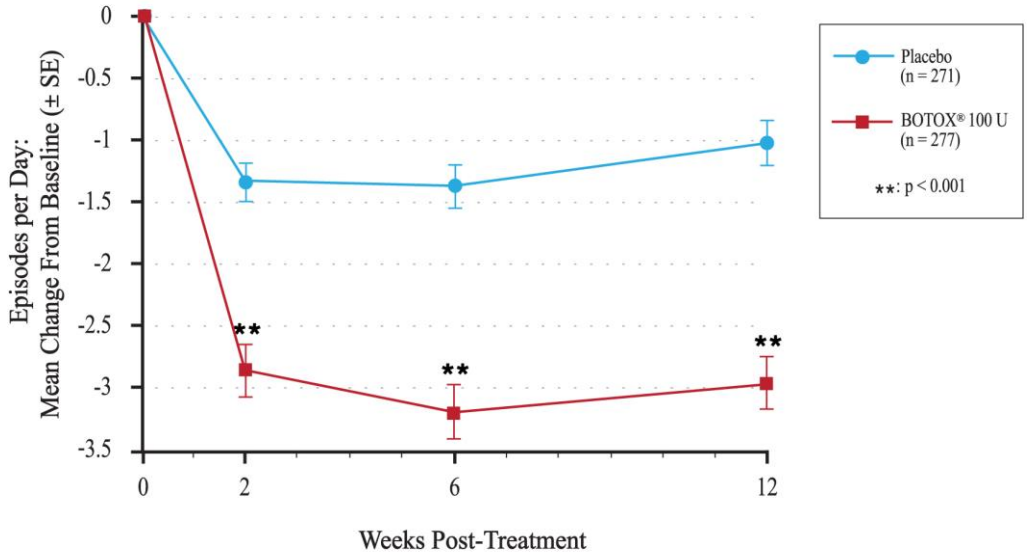


**Figure 7: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study 2**




## DETAILED PHARMACOLOGY

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

## TOXICOLOGY

*Mutagenicity Studies:*
BOTOX® (onabotulinumtoxinA for injection) was not mutagenic in the *in vitro* Ames microbial mutagen test with or without metabolic activation at a maximum concentration of 42.9 U/plate using tester strains of *Salmonella typhimurium* and *Escherichia coli*. No increases in the average mutant frequencies were seen in *in vitro* evaluations of BOTOX® at dosages as high as 43.0 U/plate (approximately 100,000 times the maximum anticipated clinical dose, based upon 360 U/60 kg person) with and without metabolic S9 activation in AS52/XPRT mammalian cells. No chromosomal aberrations were produced in *in vitro* evaluations of BOTOX® in Chinese hamster ovary cells at dosages as high as 43.0 U/kg with and without metabolic activation. No

clastogenic effects were observed in *in vivo* micronucleus evaluations of BOTOX® in mice at doses as high as six to seven times the maximum anticipated human dose.

*Fertility and Reproductive Toxicity:*
A fertility and reproductive toxicity study with BOTOX® was evaluated in rats. No effects on reproduction were observed following intramuscular injection of BOTOX® at dosages of 4 U/kg (approximately 2/3 of the maximum recommended human dose) in male rats and at dosages of 8 U/kg in female rats. Higher dosages (8 and 16 U/kg) were associated with dose-dependent reductions in fertility in male rats, and the cohabitation period was slightly increased at dosages of 16 U/kg. Altered estrous cycling (prolonged diestrus) and interrelated reductions in fertility occurred in the female rats dosed with 16 U/kg.

*Teratogenic Effects:*
The teratogenic effects of BOTOX® were evaluated in mice, rats and rabbits. No teratogenic effects were observed when presumed pregnant mice were injected intramuscularly with doses of 4 U/kg (approximately 2/3 of the maximum recommended human dose) and 8 U/kg on days 5 and 13 of gestation; however, dosages of 16 U/kg induced a slightly lower fetal body weight. No teratogenic effects were observed in rats when injected intramuscularly with doses of 16 U/kg on days 6 and 13 of gestation, and 2 U/kg/day on days 6 through 15 of gestation. In rabbits, daily injections at dosages of 0.5 U/kg/day (days 6 through 18 of gestation) and 4 and 6 U/kg (days 6 and 13 of gestation) caused death and abortions among surviving animals. External malformations were observed in the fetus in one 0.125 U/kg/day and one 2 U/kg dosage. The rabbit appears to be a more sensitive species to BOTOX®.

*Reproductive and Developmental Effects:*
The reproductive and developmental effects of BOTOX® were evaluated in rats at dose levels of 4, 8 and 16 U/kg. Muscle atrophy at the injected site, reduced body weight gains and reduced absolute feed consumption were observed following intramuscular injection of BOTOX® at dosages of 4 U/kg and higher on days 5 and 13 of presumed gestation, and day 7 of lactation. No effects on maternal reproductive performance were observed at the highest dose tested, 16 U/kg (approximately three times the maximum recommended human dose). No adverse effects on development of the pups were observed at 4 U/kg; however, higher dosages were associated with reduced pup body weight and/or pup viability at birth.

*Animal Toxicology Studies:*
There were no observable toxic effects in rats that received a single intravenous or intramuscular injection of 5 U/kg of BOTOX®, and in monkeys that received 8 U/kg intramuscularly.

In a one year study where monkeys received seven intramuscular injections (once every two months), there were no observable toxic effects at a BOTOX® dosage level of 4 U/kg (approximately 2/3 of the maximum recommended human dose). Three out of six female monkeys in the 16 U/kg group were sacrificed in extremis. This probably was a treatment-related effect of high doses of BOTOX®. Local muscle atrophy and degeneration at the injection site (expected pharmacological effects) were observed in all BOTOX® treated monkeys. There was evidence of systemic toxicity in animals treated with 8 U/kg and 16 U/kg. No antibodies were detected in the sera of animals during the study.

In a 20 week study where juvenile monkeys received a series of three im injection sessions (each session divided into four sites, distributed bilaterally into the heads of the gastrocnemius muscles, and given at 8 week intervals), the NOEL was at a BOTOX® dosage level of 8 U/kg. Local pharmacologic effects were observed in all BOTOX®-treated animals and included decreases in size and weights of the injected site (gastrocnemius muscles) and microscopic observations of muscle fiber atrophy with occasional involvement of the underlying soleus muscle. Systemic effects included a slight transient decrease in body weight gains in animals receiving 12 U/kg.

*Neurogenic Detrusor Overactivity associtated with a neurological condition*
No systemic toxicity was observed following a single intradetrusor injection of <50 Units/kg BOTOX® in rats. In a study to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 Units/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 Units/kg (~12X the human dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 Units/kg (~33X the human dose). In a 9 month repeat dose intradetrusor study (4 injections), ptosis was observed at 24 Units/kg , and mortality was observed at doses ≥24 Units/kg. No adverse effects were observed in monkeys at 12 Units/kg, which corresponds to a 3-fold greater exposure to BOTOX® than the recommended clinical dose of 200 Units for urinary incontinence due to neurogenic detrusor overactivity (based on a 50 kg person).

*Antigenicity:*
Antigenicity studies in rats and guinea pigs showed no effects. In an indirect hemagglutination assay, mice were immunized once per week for two weeks. Both the placebo (human serum albumin) and BOTOX® were antigenic when Complete Freund's Adjuvant (CFA) was used. No antigenicity was detected without the adjuvant.

*Ocular or dermal irritation:*
No ocular or dermal irritation was observed in rabbits at concentrations of BOTOX® up to 200 U/mL.

## REFERENCES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## PART III: PATIENT MEDICATION INFORMATION
## BOTOX®
## (onabotulinumtoxinA for injection)

Read this carefully before you start taking BOTOX® and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about BOTOX®.

**Serious Warnings and Precautions**

- The term "Allergan unit" upon which dosing is based is a specific measurement of toxin activity that is unique to Allergan's formulation of botulinum toxin type A. Therefore, the "Allergan units" used to describe BOTOX® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX® activity are not interchangeable with other products.
- BOTOX® should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.
- The recommended dosage and frequency of administration for BOTOX® (See **WARNINGS AND PRECAUTIONS**, **General** and **DOSAGE AND ADMINISTRATION**) should be followed.
- DISTANT SPREAD OF TOXIN EFFECT: The effects of Botox and Botox Cosmetic 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 occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

### What is BOTOX® used for:

BOTOX® works by temporarily weakening overactive muscles which may cause:

- crossed eyes (strabismus)
- persistent muscle spasms in the eyelid and face (blepharospasm)
- unnatural ankle position and walking pattern (juvenile cerebral palsy and focal spasticity)
- muscle contractions in the neck and twisting of the head (cervical dystonia)
- muscle contractions in the limbs (focal spasticity)
- leakage of urine (urinary incontinence) due to neurologic disease in adult patients with multiple sclerosis or spinal cord injury who have an inadequate response to or are intolerant of anticholinergics;
- overactive bladder with symptoms of leakage of urine (urinary incontinence), urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of anticholinergic medication.

BOTOX® can also block signals to the sweat glands thus reducing excessive sweating (hyperhidrosis).

BOTOX® can also be used to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day. In this patient population, BOTOX® has been shown to significantly reduce the number of headache days per month.

BOTOX® has been shown to reduce the amount of head turning and shoulder elevation, decrease the size and strength of the overactive muscles and reduce pain in patients with cervical dystonia.

BOTOX® has been shown to reduce the muscle contractions (focal spasticity), increase the range of move and in some patients, reduce disability related to the muscle contractions (focal spasticity), in patients with upper and lower limb muscle contractions (focal spasticity).

BOTOX® has been shown to significantly reduce leakage of urine in patients suffering from leakage of urine due to neurologic disease.

BOTOX® has been shown to significantly reduce leakage of urine and improve the quality of life of patients suffering from leakage of urine due to overactive bladder.

**How does BOTOX® work:**
BOTOX® is a muscle relaxant that is injected into the muscles or deep into the skin. It works by partially blocking the nerve impulses to any muscles that have been injected and reduces excessive contractions of these muscles. The muscle relaxation is reversible with a time limited duration of effect.

In the case of chronic migraine, it is thought that BOTOX® blocks pain signals, which indirectly block the development of a migraine.

When injected into the skin, BOTOX® works on sweat glands to reduce the amount of sweat produced.

When injected into the bladder wall, BOTOX® works on the bladder muscle to prevent leakage of urine (urinary incontinence) due to uncontrolled contractions of the bladder muscle.

**What are the ingredients in BOTOX®:**
Medicinal ingredient: OnabotulinumtoxinA for injection, ~~is~~ a sterile, form of purified botulinum neurotoxin type A complex
Non-medicinal ingredients: Albumin (human) and sodium chloride.

**Do not use BOTOX® if:**
- you are allergic or sensitive to any of the ingredients
- you have an infection in the muscles where it would normally be injected.
- you have any muscle disorders in other parts of your body, including myasthenia gravis, Eaton Lambert Syndrome or amyotrophic lateral sclerosis.

- you are being treated for leakage of urine with BOTOX® and have either a urinary tract infection or an inability to empty your bladder (and are not regularly using a catheter).
- you are not willing and able to have catheterization initiated.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take BOTOX®. Talk about any health conditions or problems you may have, including if you:**

- you have myasthenia gravis or Eaton Lambert Syndrome, amyotrophic lateral sclerosis or another muscle disorder.
- you are allergic or sensitive to BOTOX®.
- you have an infection at a proposed injection site.
- you are being treated for leakage of urine with BOTOX® and have either a urinary tract infection or a sudden inability to empty your bladder (and are not regularly using a catheter).
- you are scheduled to have surgery using a general anaesthetic.
- you are taking or are likely to take antibiotics, especially aminoglycoside antibiotics.
- you are pregnant or become pregnant while taking this drug. Repeated doses of BOTOX® given to rabbits during pregnancy have caused abortion or fetal malformations.
- you are nursing. It is not known whether this drug is excreted in human milk, but many drugs are excreted in human milk.
- you have had any previous episodes of autonomic dysreflexia, for patients being treated for leakage of urine due to neurologic disease with BOTOX®

**Other warnings you should know about:**
Seek immediate medical care if swallowing, speech or respiratory problems arise.

Tell your doctor if you experience any difficulties in swallowing food while on BOTOX®, as it could be related to the dosage. Difficulty in swallowing food, ranging from very mild to severe, can persist for 2-3 weeks after injection, or longer.

It is unlikely that this medicine will improve the range of motion of joints where the surrounding muscle has lost its ability to stretch.

BOTOX should be used when treating persistent post-stroke ankle muscle spasms in adults only if it is expected to result in improvement in function (e.g. walking) or symptoms (e.g. pain) or to help with patient care. Furthermore, for patients who may be more likely to fall, your doctor will judge if this treatment is suitable.

BOTOX should only be used for the treatment of post-stroke ankle muscle spasms following evaluation by health care professionals experienced in the management of the rehabilitation of post-stroke patients.

Tell your doctor if you are taking other medicines, including any you have bought at your pharmacy, supermarket or health food shop. If you are being treated for leakage of urine with BOTOX®, especially tell your doctor if you are taking any anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners).

If you are being treated for leakage of urine with BOTOX®, contact your doctor if you experience difficulties in voiding as catheterization may be required.

You should know that, if you are being treated for leakage of urine with BOTOX®, the injection for the treatment of your condition is performed under cystoscopy and that local anesthetic, sedation or anesthesia may be needed.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with BOTOX®:**
The effect of BOTOX® may be increased by aminoglycoside antibiotics (e.g. streptomycin, tobramycin, neomycin, gentamicin, netilmicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs that interfere with neuromuscular transmission.

**How to take BOTOX®:**
- Intramuscular Use for All Indications except Hyperhidrosis
- Intramuscular Injections into Bladder Wall for Urinary Incontinence
- Intradermal Use for Hyperhidrosis only

**Usual dose:**
BOTOX® is injected into your muscles (intramuscularly), into the bladder wall via a specific instrument (cystoscope) to inject into the bladder, or into the skin (intradermally). It is injected directly into the affected area of your body; your doctor will usually inject BOTOX® into several sites within each affected area.

A unit of BOTOX® is a dose measurement that is specific to BOTOX® and cannot be interchanged with the units used to measure other botulinum toxin products.

The dosage of BOTOX® and the duration of its effect will vary depending on the condition for which you are treated. The number of injections per muscle and the dose vary depending on the indications. Therefore, your doctor will decide how much, how often, and in which muscle(s) BOTOX® will be given to you. It is recommended that your doctor uses the lowest effective dose. The dose can be increased in subsequent treatments if needed.

If you feel that the effect of BOTOX® is not optimal, let your doctor know. There are several potential reasons for this that your doctor can assess.

Below are details corresponding to each condition.

*Persistent muscle spasms in the eyelid and face (blepharospasm)*
Your doctor may give multiple injections in the affected muscles. You will usually see an improvement within 3 days after the injection. The maximum effect is usually seen 1 to 2 weeks after treatment. The effects last approximately 3 months, after which treatment can be re administered. The treatment can be repeated indefinitely.

*Crossed eyes (strabismus)*
Your doctor may give multiple injections in the affected muscles. You will usually see an improvement within 1 - 2 days after the injection. The maximum effect is usually seen 1 week after treatment and lasts 2 – 6 weeks. The effect starts to wear off gradually over the following 2 – 6 weeks.

*Muscle contractions in the neck and twisting of the head (cervical dystonia)*
Your doctor may give multiple injections in the affected muscles, especially for lager muscles. The maximum effect is usually seen approximately 6 weeks after treatment. When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 2 months.

*Muscle contractions in the limbs (focal spasticity)*
Your doctor may give multiple injections in the affected muscles. The dose and number of injections will vary depending on a number of factors, including your needs, the muscles to be injected, the size of the muscles, severity of spasms, local muscle weakness and response to previous treatments. Your doctor may decide to use electromyographic (EMG) guidance or nerve stimulation to determine where injections should be administered in a muscle. You will usually see an improvement within the first 2 weeks after the injection. The maximum effect is usually seen about 4 to 6 weeks after treatment. When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 12 weeks.

*Unnatural ankle position and walking pattern*
Your doctor may give multiple injections in the affected muscles. Improvement usually appears within the first 2 weeks after the injection. When the effect starts to wear off, further treatment is possible, but not more often than every 3 months.

*Excessive Sweating of the Underarm*
Your doctor may give multiple injections in the underarm area. Improvement usually appears within the first 2 weeks after the injection. When the effect starts to wear off, further treatment is possible, but not more often than every 3 months.

*Chronic Migraine*
BOTOX® is injected by needle into 7 specific head and neck muscle areas. These areas may be contributing to your headaches. You doctor will determine the number of injection sites required to treat your specific condition. The recommended dose of BOTOX® ranges is 155 units in 31 sites. If your doctor thinks it is necessary, he or she may decide to inject additional units of BOTOX®. The recommended retreatment schedule is every 12 weeks.

*Leakage of Urine and Overactive Bladder*
Your doctor may give multiple injections in the bladder wall. Improvement usually appears within the first 2 weeks after the injection. When the effect starts to wear off, further treatment is possible, but not more often than every 3 months.

Lack of Response
There are several potential explanations for a lack or diminished response to an individual treatment with BOTOX®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement, patient perception of benefit compared with initial results, inappropriate storage or reconstitution, as well as neutralizing antibodies to botulinum toxin. Talk to your doctor if you feel that you had a lack of or diminished response to your treatment with BOTOX®.

**Overdose:**

| |
|---|
| In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. |

**What are possible side effects from using BOTOX®?**
These are not all the possible side effects you may feel when taking BOTOX®. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

**General**
Pain, tenderness and/or bruising at the site of injection. Malaise (generally feeling unwell), lasting up to six weeks after injection with BOTOX®. Weakness and rarely, changes in the way the heart beats, chest pain, skin rash and allergic reaction (symptoms: shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin); anaphylaxis; cardiovascular events; seizures; dysphagia; and respiratory compromise.

The following events have been reported rarely (<0.1%) since BOTOX® has been marketed: skin rash, itching, allergic reaction, and facial paralysis. There have also been rare 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.

**Blepharospasm**
Drooping of the eyelids, irritation or tearing, dry eye, not being able to close the eye, and sensitivity to light. Less commonly, inward or outward turning of the eye, inflammation of the eye, double vision, and swelling of the eyelid skin lasting several days.

**Strabismus**
Drooping of the eyelids, vertical turning of the eye, double vision, bleeding beneath the eye lids and at the front of the eye. Less commonly, bleeding behind the eye ball, piercing of the sclera (the tough skin covering part of the eye bulb), dilation of the pupil, loss of awareness of space and past pointing (the inability to place a finger on another part of the body accurately, headache, inability to focus, dizziness, discomfort/irritation of the eye, increased pressure in the eye.

**Spasticity due to Juvenile Cerebral Palsy:**
Falling, leg pain, weakness of the leg and generalised weakness. Less commonly, leg cramps, fever and knee or ankle pain.

**Cervical Dystonia**
Soreness or bruising where the injection was given, difficulty in swallowing, weakness of the neck, and less commonly, general weakness, malaise and nausea. Side effects, if they occur, tend to appear in the first week after injection, and last about two weeks.

However, in rare instances, patients may have difficulty in swallowing that could persist for longer than two weeks **after injection** and may develop into a more serious condition. Make sure you tell your doctor if you experience any difficulty in swallowing.

**Primary hyperhidrosis**
Increase in sweating in other areas of the body, headaches and pain at the injection site.

**Focal spasticity**
*Upper Limb Spasticity*
Most side effects that have been reported in patients being treated for focal spasticity were mild to moderate and got better without needing medical attention. Side effects reported include: pain in the affected limb, changes in ease of movement of the muscle, increased sensitivity to touch or pain and headache. Less common side effects include: fever, flu syndrome, weakness or a loss of energy, joint pain, skin problems, nausea, 'pins & needles', itching and lack of coordination.

*Lower Limb Spasticity*
Fall and pain in extremity were the common side effects reported in patients being treated for lower limb spasticity in clinical trials.

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | |
|---|---|---|---|
| Symptom / effect | | Talk with your healthcare professional | |
| | | Only if severe | In all cases |
| Very Coommon | Joint pain | ✓ | |

**Chronic migraine**
The following common events were reported in patients being treated for chronic migraine in clinical trials: headache, facial muscle weakness, drooping of the eyelids, muscle spasm, muscle tightness, injection pain and rash.

**Urinary Incontinence Due to Neurologic Disease**

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | |
|---|---|---|---|
| Symptom / effect | | Talk with your healthcare professional | |
| | | Only if severe | In all cases |
| Very Common | Urinary tract infection | | ✓ |
| | Inability to empty your bladder (urinary retention) | | ✓ |

Common side effects: problems with walking, fall, muscle weakness, muscle spasm, tiredness, difficulty sleeping (insomnia), constipation, blood in the urine after the injection, painful urination after the injection.

**Overactive Bladder**

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | |
|---|---|---|---|
| Symptom / effect | | Talk with your healthcare professional | |
| | | Only if severe | In all cases |
| Very Common | Urinary tract infection | | ✓ |
| | Painful urination after the injection* | | ✓ |

Common side effects: bacteria in the urine; inability to empty your bladder (urinary

retention), incomplete emptying of the bladder, frequent daytime urination, blood in the urine after the injection**.
*This side effect may also be related to the injection procedure.
**This side effect is only related to the injection procedure.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
**3 ways to report**:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**
Store the vacuum-dried product either in a refrigerator at 2º - 8ºC, or in a freezer at or below -5º C.

Keep out of reach and sight of children.

**If you want more information about BOTOX®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.botox.ca , or by calling 1-800-668-6424.

This leaflet was prepared by Allergan Inc.
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