BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex

Description: BOTOX® (Botulinum Toxin Type A) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain Clostridium botulinum type A, and intended for intramuscular, intradetrusor and intradermal use. It is purified from the culture solution as an approximately 900 kD molecular weight complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Human Albumin and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

The primary release procedure for **BOTOX®** uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products **BOTOX®**. One Unit of **BOTOX®** corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of **BOTOX®** cannot be compared to nor converted into Units of any other Botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of **BOTOX®** is approximately 20Units/nanogram of neurotoxin protein complex
Each vial of **BOTOX®** 50 U contains 50 units (U) of *Clostridium botulinum* type A neurotoxin complex, 0.25 milligrams of Human Albumin, and 0.45 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

Each vial of **BOTOX®** 100 U contains 100 units (U) of *Clostridium botulinum* type A neurotoxin complex, 0.5 milligrams of Human Albumin, and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

Each vial of **BOTOX®** 200 U contains 200 units (U) of *Clostridium botulinum* type A neurotoxin complex, 1 milligrams of Human Albumin, and 1.8 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

Pharmacodynamic Properties:

Mechanism of Action:

BOTOX® blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the light chain toxin is released into the cytosol where it cleaves SNAP-25. This latter process is accompanied by progressive inhibition of acetylcholine release; clinical signs usually manifest within 2-3 days, with peak effect seen within 5-6 weeks of injection. 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. .

Recovery after intramuscular injection takes place normally within 12 weeks as new nerve terminals sprout and allow for reconnection of the neuron with the endplates. However, the sprouts are partially effective and subsequently regress while the primary neuromuscular junction reactivates. After intradermal injection, where the target is the eccrine sweat glands, the effect lasted an average of 6-10 months after the first injection in patients treated with 50 Units per axilla. However, in 27.5% of patients the duration of effect was one year or greater. Recovery of the sympathetic cholinergic nerve endings that innervate sweat glands after intradermal injection with BOTOX® has not been studied

BOTOX® blocks the release 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 confirmed by pre-clinical and clinical studies.

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

Pharmacokinetics

General characteristics of the active substance:

Distribution studies in rats indicate minimal muscular diffusion of I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabeled material in the muscle declined at a half-life of approximately 10 hours. At the injection site the radioactive material was mainly in the form of large macromolecules, whereas very little of the radioactivity reaching the systemic circulation was TCA-precipitable, suggesting a minimal systemic exposure of toxin following gastrocnemius muscle injection of I-botulinum neurotoxin A complex. Within 24 hours of dosing, 60% of the radioactivity was excreted in the urine. The toxin is probably metabolized by proteases and the molecular components cycled through normal metabolic pathways.

Classical absorption, distribution, biotransformation and elimination studies on the active substance have not 2014 been performed due to the nature of this product.

Characteristics in patients:

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.

Clinical Studies:

Cervical dystonia:

A phase 3 randomized, multi-center, double blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received **BOTOX®** in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of **BOTOX®.** Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

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

Table 1: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

	Placebo (N=82)	**BOTOX (N=88)**	**95% CI on Difference**
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[a,b]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.

[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.

[c] Confidence intervals are based on the t-distribution

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

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

Table 2: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

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

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

There were several randomized studies conducted prior to the phase 3 study which was supportive but not adequately designed to assess or quantitatively estimate the efficacy of **BOTOX®**.

Blepharospasm/Hemifacial Spasm: A randomized, multicenter, double-blind, parallel group clinical study comparing the safety and efficacy of 2 formulations of BOTOX® (active substance derived from different Master Cell Banks, one of which is the current BOTOX® formulation) was conducted in patients with benign essential blepharospasm. The study enrolled patients with previous exposure to BOTOX® and treatment consisted of a single course of injections in the orbicularis oculi muscle of both eyes. The dose (maximum permitted was 100 Units) and injection sites were determined by the investigator based on the patients' response to previous BOTOX® exposure. Patients were observed for a period of 12 weeks after treatment.

There were 98 patients enrolled in the study (48 in the current BOTOX® formulation group). The treatment success rate was measured using a five point rating scale from 0 to 4 where 0 was equal to "none" and 4 equal to "severe" incapacitating spasm of eyelids and possibly other facial muscles. A drop to a score of ≤ 2 in both eyes was considered a treatment success. The primary time point was at week 4. The average dose received by the patients was 33 Units per eye, injected at 3 to 15 sites. Comparable with the earlier BOTOX® formulation, the treatment success rate with the current BOTOX® formulation was approximately 90% at week 4.

In an open study, 56 patients with hemifacial spasm were injected with an initial dose of 10 to 50 Units followed by 22 weeks of observation. Patients who did not show any improvement at Week 4 were re-injected (5 to 50 Units). Subjects were observed at week 2, 4 (if re-treatment required), 6, 14 and 22. The clinical effects were assessed for the various upper and lower facial muscles at each visit.

All 56 patients showed improvement, and 62.5% (35/56) showed marked improvement. When the upper facial muscles were evaluated improvement was observed in all patients. When the lower facial muscles were evaluated all but 2 patients were considered responders

Chronic migraine:

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

Table 3: Week 24 Key Efficacy Variables for Study 1 and Study 2

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

* Significantly different from placebo ($p<0.05$)

Patients treated with **BOTOX®** had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1, and all timepoints from Week 4 to Week 24 in Study 2, compared to placebo-treated patients.

Overactive Bladder (OAB)

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for **BOTOX®** 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 4 and 5, and Figures 1 and 2.

Table 4: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

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

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

Table 5: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

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

*LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

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

** Primary timepoint

[a] Primary variable

[b] Secondary variable

Figure 1: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-1

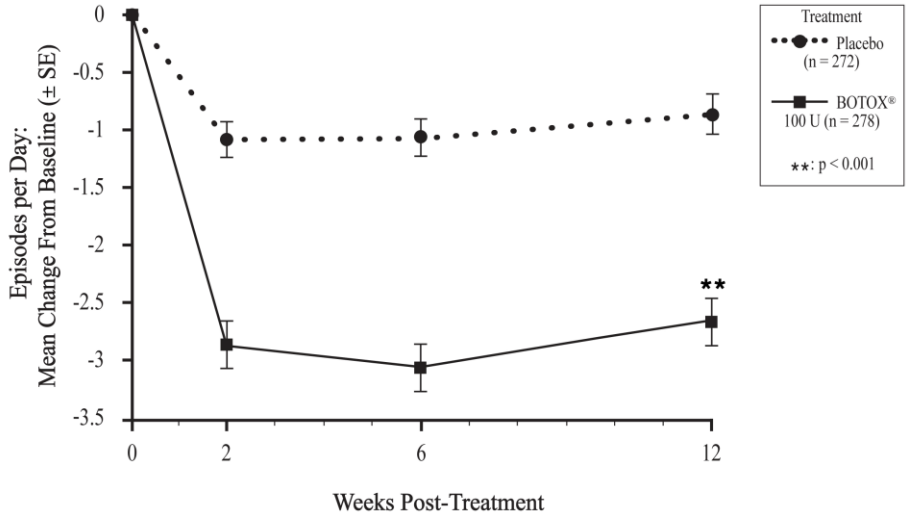
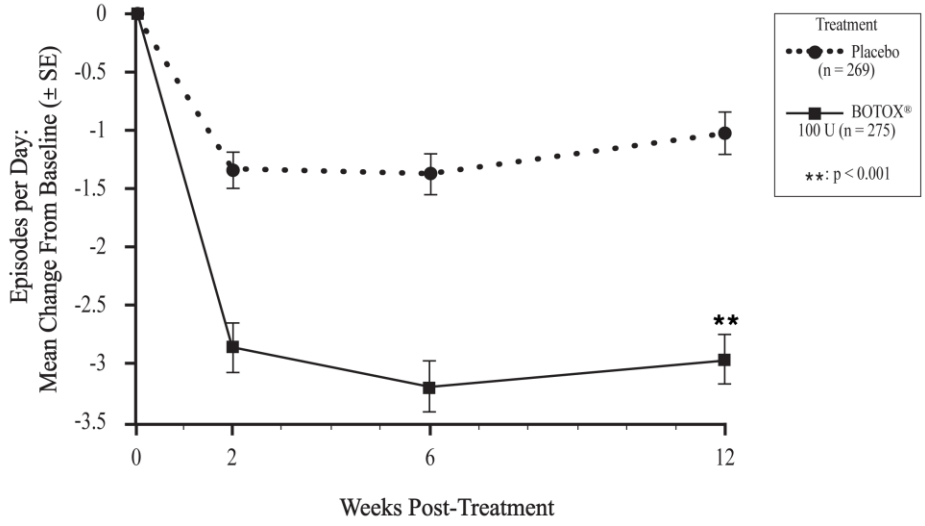


Figure 2: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-2



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

In the pivotal studies, none of the 615 (0%) patients with analyzed specimens developed the presence of serum neutralizing antibodies to BOTOX®. 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

Neurogenic Detrusor Overactivity (NDO)

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

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for **BOTOX®** (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 6 and 7, and Figures 3 and 4.

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

Table 6: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_20) Study NDO-1

	BOTOX® 200 Units	**Placebo**	**Treatment Difference***	**p-value***
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	134	146		
Mean Baseline	32.3	28.3		
Mean Change* at Week 2	-15.3	-10.0	-5.3	–
Mean Change* at Week 6**	-19.9	-10.6	-9.2 (-13.1, -5.3)	p<0.001
Mean Change* at Week 12	-19.8	-8.8	-11.0	–
Maximum Cystometric Capacity[b] (mL)				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change* at Week 6**	135.9	12.1	123.9 (89.1, 158.7)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change* at Week 6**	-28.1	-3.7	-24.4	–

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

** Primary timepoint

[a] Primary endpoint

[b] Secondary endpoint

Table 7: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH_20) in Study NDO-2

	BOTOX® 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes[a]				
N	91	91		
Mean Baseline	32.7	36.8		
Mean Change* at Week 2	-18.0	-7.9	-10.1	–
Mean Change* at Week 6**	-19.6	-10.8	-8.8 (-14.5, -3.0)	p=0.003
Mean Change* at Week 12	-19.6	-10.7	-8.9	–
Maximum Cystometric Capacity[b] (mL)				
N	88	85		
Mean Baseline	239.6	253.8		
Mean Change* at Week 6**	150.8	2.8	148.0 (101.8, 194.2)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction[b] (cmH_2O)				
N	29	68		
Mean Baseline	65.6	43.7		
Mean Change* at Week 6**	-28.7	2.1	-30.7	–

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

** Primary timepoint

[a] Primary endpoint

[b] Secondary endpoint

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

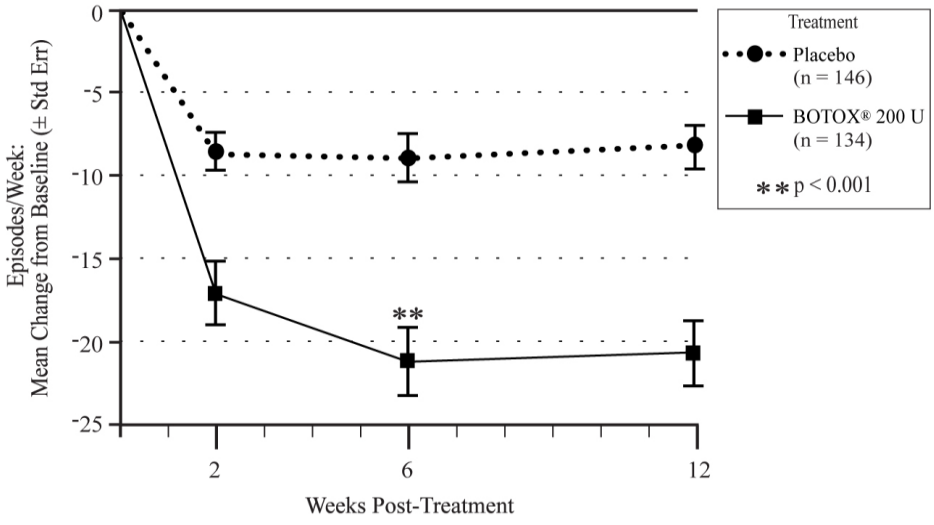
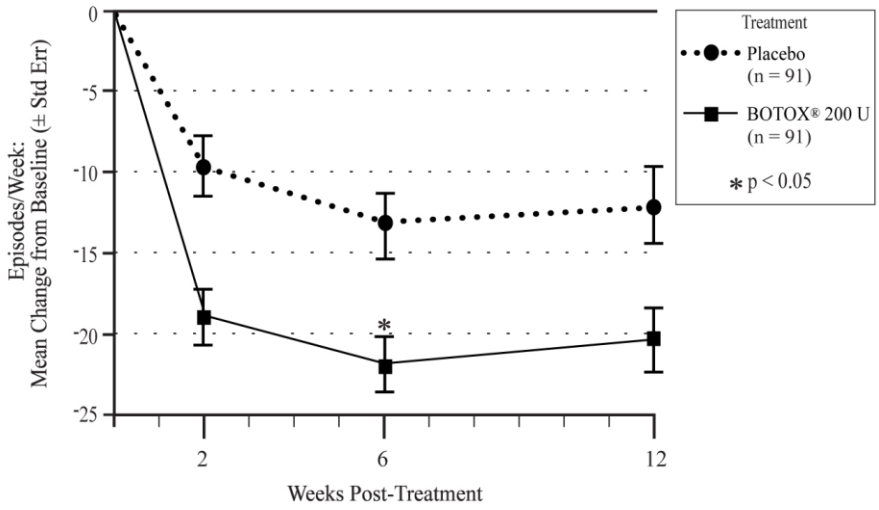


Figure 4: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2



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

In the pivotal studies (300 Units and 200 Units), 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.

STUDY 3 (NDO-3)

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

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

Glabellar Lines:

Two phase 3 randomized, multi-center, double-blind, placebo-controlled trials of identical design were conducted to evaluate **BOTOX®** for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. The trials enrolled healthy adults (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Subjects were excluded if they had ptosis, deep dermal scarring, or an inability to substantially lessen glabellar lines even by physically spreading them apart. Subjects received a single treatment with **BOTOX®** (N=405, combined trials) or placebo (N=132, combined trials). Injection volume was 0.1 mL/injection site, for a dose/injection site in the active treatment groups of 4 Units. Subjects were injected intramuscularly in five sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units.

The co-primary efficacy endpoints were the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines, both at Day 30 post-injection. For the investigator rating, using a 4-point grading scale (0=none, 3=severe) a responder was defined as having a severity grade of 0 or 1. For the subject's global assessment of change, the ratings were from +4 (complete improvement) to -4 (very marked worsening). A responder was defined as having a grade of at least +2 (moderate improvement). After completion of the randomized studies, subjects were offered participation in an open label, repeat treatment study to assess the safety of repeated treatment sessions.

The combined results of these two efficacy trials are presented here. The mean age was 46 years, with 32 subjects (6%) ≥ 65 years of age. Most of the subjects were women (82%), and Caucasian (84%). At baseline, 210 subjects (39%) had glabellar line severity scores at rest of moderate or severe.

In these trials, the severity of glabellar lines was reduced for up to 120 days in the **BOTOX®** group compared to the placebo group as measured both by investigator rating of glabellar line severity at maximum frown, and by subject's global assessment of change in appearance of glabellar lines.

Table 8: Investigator's Assessment of Glabellar Line Severity at Maximum Frown – Responder Rates (% and Number of Subjects with Severity of None or Mild)

Day	BOTOX	Placebo	Difference[a]
7	74% 299/405	6% 8/132	68% (62, 74)
30[b]	80% 325/405	3% 4/132	77% (72, 82)
60	70% 283/403	2% 2/130	69% (64, 74)
90	48% 192/403	2% 3/128	45% (40, 51)
120	25% 102/403	2% 2/128	24% (19, 29)

[a] 95% confidence intervals are shown in parenthesis

[b] Day 30: Co-Primary Efficacy Time point, p<0.001

Table 9: Subject's Assessment of Change in Appearance of Glabellar Lines – Responder Rates (% and Number of Subjects with at Least Moderate Improvement)

Day	BOTOX	Placebo	Difference[a]
7	82% 334/405	9% 12/132	73% (68, 80)
30[b]	89% 362/405	7% 9/132	83% (77, 88)
60	82% 330/403	4% 5/130	78% (73, 83)
90	63% 254/403	3% 4/128	60% (54, 66)
120	39% 157/403	1% 1/128	38% (33, 43)

[a] 95% confidence intervals are shown in parenthesis

[b] Day 30: Co-Primary Efficacy Time point, p<0.001

In the subset of subjects with resting severity scores of moderate or severe, the investigator assessment of a resting severity of mild or none at Day 30 was also achieved by more **BOTOX®** treated subjects (74%, 119/161) than placebo treated subjects (20%, 10/49). Analysis of the limited number of subjects 65 years or older suggested a lower treatment-associated response compared to subjects less than 65 years of age

Table 10: Investigator's and Subject's Assessment – Responder Rates for Subjects < 65 and ≥ 65 Years of Age at Day 30

Assessment	Age Group	BOTOX (N=405)	Placebo (N=132)	Difference[a]
Investigators (maximal frown)	<65	83% 316/382	2% 2/123	81% (77, 86)
Subjects	<65	91% 346/382	7% 8/123	84% (79, 90)
Investigators (maximal frown)	≥65	39% 9/23	22% 2/9	17% (-17, 51)
Subjects	≥65	70% 16/23	11% 1/9	58% (31, 86)

[a] 95% confidence intervals are shown in parenthesis

Exploratory analyses by gender suggested that responder rates in the **BOTOX®** treated group were higher for women than for men for both the investigator assessment (Day 30; 85% of 334 women, 59% of 71 men) and the Subject Assessment (Day 30; 93% of women, 72% of men). In the limited number of non-Caucasian subjects (n=64 in the **BOTOX®** treated group) the responder rates were similar to those observed in the Caucasian subjects.

Hyperkinetic Facial Lines

Crow's Feet Lines

Three phase 3 multicenter, randomized, double-blind, placebo-controlled studies evaluated BOTOX® (N=934, randomized to receive any BOTOX® treatment) for the temporary improvement in the appearance of moderate to severe crow's feet lines (CFL). Study 1 assessed BOTOX® treatment of CFL alone; Studies 2 and 3 also assessed simultaneous treatment of CFL and glabellar lines (GL). All studies enrolled healthy adults with moderate to severe CFL at maximum smile at baseline; Studies 2 and 3 also required patients to have moderate to severe GL at maximum frown at baseline.

Focal Lower Limb Spasticity associated with Pediatric Cerebral Palsy – Equinus

A three-month, double-blind, placebo-controlled parallel study was conducted in cerebral palsy children, aged 2 to 16 years with equinus ankle position. Seventy-two were administered 4 Units/kg body weight of Botox® into the medial and lateral heads of the gastrocnemius at baseline (2 Units/kg/muscle), for hemiplegic patients and 1Unit/kg/muscle for diplegic patients) and again at 4 weeks. The cumulative dose of Botox® over 4 weeks was 2-4 Units/kg/muscle and overall 8 Units/kg body weight up to a maximum of 200 Units per visit during a 30 day period. Botox® was significantly more effective than placebo as assessed by improvement of 2 Units or more on the composite score of Physician's Rating Scale (PRS) of dynamic gait (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® patients versus 25%, 27%, 25% and 32% of placebo patients at weeks 2, 4, 8 and 12, respectively. Of the individual assessments included on the PRS, a significantly greater number of Botox® patients versus placebo patients had improvements in gait pattern (weeks 2, 8 and 12) and ankle position (weeks 2, 4, 8 and 12).

In the 39 month long-term, open-label follow up of these patients, the medial and lateral gastrocnemius muscles were injected at a dose of 2 Units/kg/muscle with a maximum total dose of 200 Units of Botox® into the medial and lateral heads of the gastrocnemius, and then as needed thereafter. Of the 207 patients evaluated; 155 patients were followed for 12 months, 100 for 18 months, 42 for 2 years and 7 for up to 3 years. The percent of patients who showed an improvement based on the PRS of dynamic gait pattern ranged from 41% to 67% over the 3-year period. Of the individual assessments which were included in the PRS, significant improvements were seen at every visit over the 3-year period.

Focal Spasticity associated with Stroke in Adults

Allergan has completed 9 studies in lower limb post-stroke spasticity patients, including 7 double-blind, placebo-controlled studies (4 out of 7 studies included an open label follow-up period), 1 double-blind extension study and 1 open-label study. 1164 post-stroke patients with lower limb spasticity were enrolled in these completed studies; 1082 patients in the "All BOTOX® treated" population were treated with doses of 25 Units to 800 Units and 498 patients received placebo. Two phase 3 placebo-controlled studies [Study 1 (BTX108512) and Study 2 (191622-116)] were shown to demonstrate statistically and clinically significant improvement in ankle tone as measured by the modified Ashworth Scale (MAS; a measure of the physiological effect on muscles) and the Physician Global Assessment (CGI; a measure of the clinical effect of treatment on the patient's overall status). In addition, Study 2 demonstrated significant improvements in the toe flexor tone (flexor hallucis longus and flexor digitorum longus).

Study 1

A double-blind, placebo-controlled, randomised, multi-centre Phase 3 clinical study was conducted in adult post-stroke patients with lower limb spasticity affecting the ankle. A total of 120 patients were randomised to receive either BOTOX® (n=58) (total dose of 300 Units) or placebo (n=62).

Significant improvement compared to placebo was observed in the primary endpoint for the overall change from baseline up to week 12 in Modified Ashworth Scale (MAS) ankle score, which was calculated using the area under the curve (AUC) approach. The Modified Ashworth Scale uses a similar scoring system as the Ashworth Scale (see Table 1 below). Significant improvements compared to placebo were also observed for the mean change from baseline in MAS ankle score at individual post-treatment visits at weeks 4, 6 and 8. The proportion of responders (patients with at least a 1 grade improvement) was also significantly higher than in placebo treated patients at these visits. BOTOX® treatment was also associated with significant improvement in the investigator's clinical global impression (CGI) of functional disability compared to placebo. Muscle tone reduction was clinically meaningful, as demonstrated by significant correlations with investigator and patient global assessments.

Table 11:Ashworth Scale and Modified Ashworth Scale (possible scores range from 0 to 4):

Ashworth Scale		Modified Ashworth Scale (MAS)	
Score	**Definition**	**Score**	**Definition**
0	No increase in (muscle) tone	0	No increase in muscle tone
1	Slight increase in (muscle) tone, giving a catch (and release) when the limb was moved in flexion or extension	1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM) when the affected part(s) is (are) moved in flexion or extension
		1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in (muscle) tone but limb easily flexed (or moves easily)	2	More marked increase in muscle tone through most of the ROM, but affected parts easily moved
3	Considerable increase in tone, passive movement difficult	3	Considerable increase in muscle tone, passive movement difficult
4	Limb rigid in flexion or extension	4	Affected part(s) rigid in flexion or extension

Results from the phase 3 study are presented below.

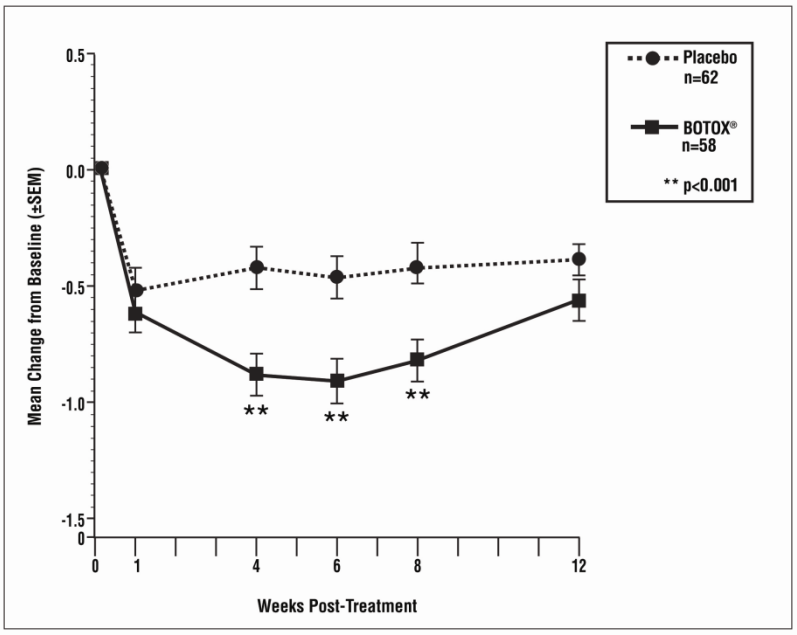
Table 12:Primary and Key Secondary Efficacy Endpoints

	BOTOX® (N=58)	**Placebo (N=62)**	**P-value**
Mean AUC in MAS Score			
AUC (day 0 to week 12)	-8.5	-5.1	0.006
Mean Change from Baseline in MAS Score			
Baseline	3.28	3.24	
Week 1	-0.61	-0.52	0.222
Week 4	-0.88	-0.43	< 0.001
Week 6	-0.91	-0.47	< 0.001
Week 8	-0.82	-0.43	< 0.001
Week 12	-0.56	-0.40	0.240
Percentage of Responders*			
Week 1	52.6%	38.7%	0.128
Week 4	67.9%	30.6%	< 0.001
Week 6	68.4%	36.1%	< 0.001
Week 8	66.7%	32.8%	< 0.001
Week 12	44.4%	34.4%	0.272

*Patients with at least a 1 grade improvement from baseline in MAS score

A consistent response was observed with re-treatment.

Figure 5:Mean Change from Baseline MAS Ankle Score (±SEM)



Study 2:**Error! Reference source not found.**

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) with 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 (see Table 1). 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.

Table 13: Study Medication Dose and Injection Sites

Muscles Injected	BOTOX® (Units)	Number of Injection Sites
Mandatory Ankle Muscles Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
Optional Muscles Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

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.

Statistically and clinically significant between-group differences for BOTOX over placebo were demonstrated for the primary efficacy measures of MAS and key secondary measure of CGI and are presented in Table .

Table 14: Primary and Key Secondary Efficacy Endpoints

	BOTOX® 300 to 400 Units (ITT) (N=233)	**Placebo (N=235)**
Mean Changes from Baseline in Ankle Plantar Flexors in MAS Score		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7
Mean Change in Toe Flexors in MAS Score		
FHL Week 4 and 6 Average	-1.0*	-0.6
FDL + FDB Week 4 and 6 Average	-0.9	-0.8

*Significantly different from placebo (p<0.05)

FHL = flexor hallucis longus; FDL = flexor digitorum longus; FDB = flexor digitorum brevis

Statistically significant improvements in MAS change from baseline (

Figure) and CGI by Physician (Figure) for BOTOX® were observed at weeks 2,4, and 6, compared to placebo.

Figure 6: Modified Ashworth Scale Ankle Score for Study 2 – Mean Change from Baseline by Visit

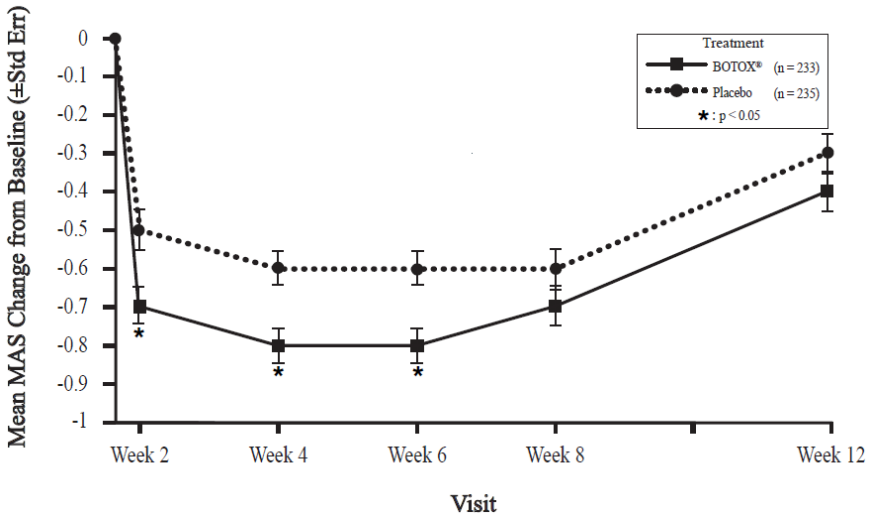
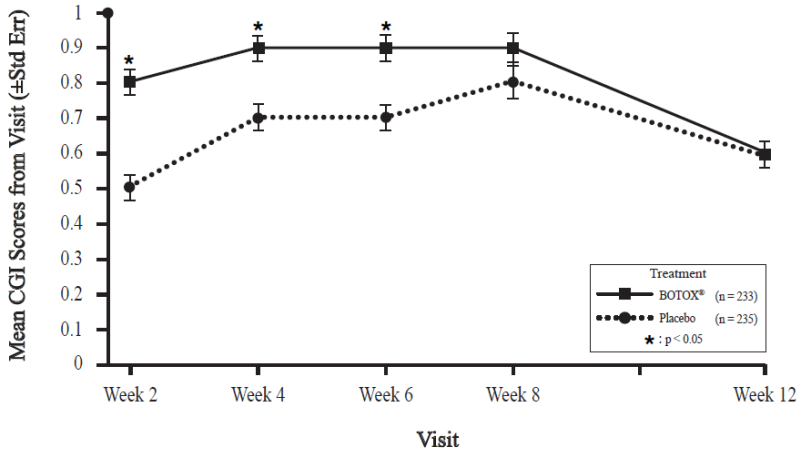


Figure 7: Clinical Global Impression by Physician for Study 2 – Mean Scores by Visit



Primary Hyperhidrosis of the Axillae

A double-blind, single-treatment cycle, multicenter clinical study was conducted in patients presenting with persistent bilateral primary axillary hyperhidrosis defined as baseline gravimetric measurement of at least 50 mg spontaneous sweat production in each axilla over 5 minutes at room temperature, at rest. Three hundred and twenty patients 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. At the primary endpoint, week 4 post-injection, the response rate in the BOTOX® group was 93.8% compared with 35.9% in the placebo group ($p<0.001$). The incidence of responders among BOTOX® treated patients continued to be significantly higher ($p<0.001$) than placebo treated patients at all post-treatment time points for up to 16 weeks.

Indications and Usage:

BOTOX® is indicated for the management of: blepharospasm, cervical dystonia, hemifacial spasm and associated focal dystonias.

BOTOX® is indicated for the treatment of focal spasticity:

• Associated with dynamic equinus foot deformity due to spasticity in ambulant pediatric cerebral palsy patients, two years of age or older.

• In adult post stroke patients.

BOTOX® is indicated for the treatment of Glabellar lines and Hyperkinetic facial lines.

BOTOX® is also indicated for the treatment of Hyperhidrosis.

BOTOX® is indicated for prophylaxis of headaches in adults with chronic migraine.

BOTOX® is indicated for the treatment of adults with urinary incontinence due to detrusor overactivity e.g., spinal cord injury (SCI) or multiple sclerosis (MS) (Neurogenic Detrusor Overactivity [NDO]) and adults with urinary incontinence due to Overactive Bladder (OAB) who have an inadequate response to or are intolerant of an anticholinergic medication.

Contraindications:

Known Hypersensitivity to Botulinum Toxin

BOTOX® is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or any of the t components in the formulation.

Infection at the Injection Site(s)

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

Urinary Tract Infection or Urinary Retention

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

Warnings and Precautions:

General

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering **BOTOX®** .

Caution should be exercised 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.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, 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.

Lack of Interchangeability between Botulinum Toxin Products

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

Spread of Toxin Effect

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

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

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

Injections In or Near Vulnerable Anatomic Structures

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. Safety and effectiveness have not been established for indications pertaining to these injection sites. Some patients had pre-existing dysphagia or significant debility. 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.

Serious Adverse Reactions with Unapproved Use

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

Hypersensitivity Reactions

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

Pre-Existing Neuromuscular Disorders

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 junctional 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 therapeutic 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.

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX®** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved

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

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

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

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin

Pulmonary Effects of BOTOX® in Patients with Compromised Respiratory Status Treated for Neurogenic Detrusor Overactivity (NDO)

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV_1 40-80% of predicted value and $FEV_1/FVC \leq 0.75$), the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table11).

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

	BOTOX 360 Units		**BOTOX 240 Units**		**Placebo**	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX®** than in patients treated with placebo

In a double-blind, placebo-controlled, parallel group study in adult patients with neurogenic detrusor overactivity and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with **BOTOX®** than in patients treated with placebo (see Table below).

Table 16: Number and percent of patients experiencing at least a 15% or 20% decrease in FVC from baseline at Week 2, 6, 12 post-injection with **BOTOX®** or placebo

	BOTOX® 200 Units		**Placebo**	
	≥15%	≥20%	≥15%	≥20%
Week 2	0/15 (0%)	0/15 (0%)	1/11 (9%)	0/11 (0%)
Week 6	2/13 (15%)	1/13 (8%)	0/12 (0%)	0/12 (0%)
Week 12	0/12 (0%)	0/12 (0%)	0/7 (0%)	0/7 (0%)

Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm/Hemifacial Spasm

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

Glabellar Lines and Hyperkinetic Lines

Reduced blinking from **BOTOX®** injection of the orbicularis oculi muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve VII disorders. Caution should be used when BOTOX® treatment is used in patients who have an inflammation at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart.

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

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

Focal Spasticity associated with Pediatric Cerebral Palsy and Focal Spasticity associated with Stroke in Adults

BOTOX® is a treatment of focal 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 not be used for the treatment of focal lower limb spasticity in adult post-stroke patients if muscle tone reduction is not 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.187

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.187

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. 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.

Autonomic Dysreflexia in Patients Treated for Neurogenic Detrusor Overactivity (NDO)

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

Urinary Tract Infections in Patients with Overactive Bladder (OAB)

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

Urinary Retention in Patients Treated for Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)

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

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

The incidence and duration of urinary retention is described below for patients with overactive bladder and neurogenic detrusor overactivity who received **BOTOX®** or placebo injections.

Overactive Bladder (OAB)

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with **BOTOX®** or placebo is shown in Table 17. The duration of post-injection catheterization for those who developed urinary retention is also shown below.

Table 17: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials in OAB

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

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown below:

Table 18: Proportion of Patients Experiencing Urinary Retention following an injection in double-blind, placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX® 100 Units (N=81)	Placebo (N=69)	**BOTOX®** 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Neurogenic Detrusor Overactivity (NDO)

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

Table 19: Proportion of Patients not using CIC at baseline and then Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials

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

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

Table 20: Proportion of Patients by Etiology (MS and SCI) not using CIC at baseline and then Catheterizing for Urinary Retention following an injection in double-blind, placebo-controlled clinical trials

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

Primary Hyperhidrosis of the Axillae

Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism or pheochromocytoma) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Human Albumin and Transmission of Viral Diseases

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) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

Drug Interactions:

Co-administration of **BOTOX®** and aminoglycosides6 or other agents interfering with neuromuscular transmission (e.g., neuromuscular blocking agents) should only be performed with caution as the effect of the toxin may be potentiated. No specific tests have been carried out to establish the possibility of clinical interaction with other medicinal products. No drug interactions of clinical significance have been reported.

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

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

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX®**.

Use In Specific Populations

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. Studies in animals have shown reproductive toxicity. **BOTOX®** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If the use of BOTOX® is determined to be warranted during pregnancy, or if the patient becomes pregnant while taking BOTOX®, the patient should be apprised of the potential risks.

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

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

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

Nursing Mothers

It is not known whether **BOTOX®** is excreted in human milk. Because many drugs are excreted in human milk. The use of BOTOX® during lactation is not recommended.

Pediatric Use

There have been 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 effects from the site of injection have been very rarely reported in pediatric patients with co-morbidities, predominately with cerebral palsy who received >8 Units/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.

Safety and efficacy of BOTOX® have not been established in children below the age of 2 years for cerebral palsy; for children below the age of 12 years for blepharospasm, hemifacial spasm, or hyperhidrosis; for patients below the age of 16 years for cervical dystonia; or for patients below the age of 18 years for adult spasticity associated with stroke, headaches in chronic migraine, overactive bladder, neurogenic detrusor overactivity,

Geriatric Use

Generally, clinical studies of BOTOX® did not identify differences in responses between the elderly and younger patients. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

Effects on Ability to Drive and Use Machines

Asthenia, muscle weakness**,** dizziness and visual disturbance have been reported after treatment of BOTOX® and could make driving or using machines dangerous.

Adverse Reactions

General

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 and/or muscles remote from the site of injection have been reported.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, 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.)

Clinical Trials Experience

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

Overactive Bladder (OAB)

The following rates were reported in double-blind, placebo-controlled, pivotal Phase 3 studies with BOTOX® 100 Units during the complete treatment cycle of the clinical trials:

Infections and infestations
Very common: Urinary tract infection
Common: Bacteriuria
Renal and urinary disorders
Very Common: Dysuria
Common: Urinary retention, pollakiuria
Investigations
Common: Residual urine volume*
elevated PVR not requiring catheterization

Procedure-related adverse reactions that occurred with a common frequency were dysuria and hematuria.
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.

Neurogenic Detrusor Overactivity (NDO)

The following rates in double-blind studies with BOTOX® 200 Units were reported during the complete treatment cycle (median duration of 44 weeks of exposure) of the, placebo controlled clinical studies

Infections and infestations
Very common: Urinary tract infection
Psychiatric disorders
Common: Insomnia
Gastrointestinal disorders
Common: Constipation
Musculoskeletal and connective tissue disorders
Common: Muscular weakness, muscle spasm
Renal and urinary disorders
Very common: Urinary retention
Common: Hematuria*, dysuria*, bladder diverticulum
General disorders and administration site conditions
Common: Fatigue, gait disturbance
Injury, poisoning and procedural complications
Common: Autonomic dysreflexia*, fall
** procedure-related adverse reactions*
No change was observed in the overall safety profile with repeat dosing.

Chronic Migraine

Safety data were compiled from two double-blind, placebo-controlled studies involving 687 patients treated with 155 Units - 195 Units of BOTOX®. The following adverse reactions were reported:

Nervous system disorders
Common: Headache, migraine, facial paresis
Eye disorders
Common: Eyelid ptosis
Gastrointestinal disorders
Uncommon: Dysphagia
General disorders and administration site conditions
Common: Injection site pain
Skin and subcutaneous tissue disorders
Common: Pruritus, rash
Uncommon: Pain of skin
Musculoskeletal and connective tissue disorders
Common: Neck pain, musculoskeletal stiffness, muscular weakness, myalgia, musculoskeletal pain, muscle spasms, muscle tightness
Uncommon: Pain in jaw

Migraine, including worsening migraine, was reported in 3.8% of BOTOX® and 2.6% of placebo patients, typically occurring within the first month after treatment. These reactions did not consistently reoccur with subsequent treatment cycles, and the overall incidence decreased with repeated treatments.

The discontinuation rate due to adverse events in these phase 3 trials was 3.8% for BOTOX® vs. 1.2% for placebo.

Cervical Dystonia

Safety data were 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 disorder

Common: Dizziness, hypertonia, hypoesthesia, somnolence, headache

Eye disorder

Uncommon: Diplopia, eyelid ptosis

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnea

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 condition

Very common: Pain

Common: Asthenia, malaise, influenza like illness

Uncommon: Pyrexia

Focal Upper Limb Spasticity associated with Pediatric Cerebral Palsy

In 74 children treated for upper limb spasticity, the following adverse reactions were reported:

Infections and infestations

Common: Influenza, pneumonia

Nervous system disorders

Common: Clumsiness, hypokinesia

Musculoskeletal and connective tissue disorders

Common: Muscular weakness, muscle spasms, trigger finger

Renal and urinary disorders

Common: Pollakiuria

Gastrointestinal disorders

Common: Vomiting

Injury, poisoning and procedural complications

Common: Joint dislocation, fall, contusion

General disorders and administration site conditions

Very common: Injection site discomfort

Common: Injection site bruising, injection site pain

Focal Lower Limb Spasticity associated with Pediatric Cerebral Palsy

Safety data were 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 Upper Limb Spasticity associated with Stroke in Adults
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
Uncommon: Hypoesthesia, headache, paresthesia
Vascular disorders
Uncommon: Orthostatic hypotension
Gastrointestinal disorders
Uncommon: Nausea
Skin and subcutaneous tissue disorders
Common: Ecchymosis
Uncommon: Dermatitis, pruritus, rash
Musculoskeletal and connective tissue disorders
Common: Pain in extremity, muscular weakness
Uncommon: Arthralgia, bursitis
General disorders and administration site conditions
Common: Injection site pain, pyrexia, influenza like illness
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise

Focal Lower Limb Spasticity (Ankle) associated with Stroke in Adults
The most frequently reported adverse reactions reported by ≥1% of BOTOX treated patients and more frequent than in placebo-treated patients in adult lower limb spasticity double-blind, placebo-controlled clinical trials are listed below.

General disorders and administration site conditions
Common: Peripheral edema
Musculoskeletal and connective tissue disorders
Common: Arthralgia, Musculoskeletal stiffness
Skin and subcutaneous tissue disorders
Common: Rash

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

Blepharospasm

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

Nervous system disorders

Uncommon: Dizziness, facial palsy

Eye disorders

Very common: Eyelid ptosis.

Common: Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, lacrimation increase

Uncommon: Keratitis, ectropion, diplopia, entropion, vision blurred

Rare: Eyelid edema

Very rare Ulcerative keratitis, corneal epithelium defect, corneal perforation

Skin and subcutaneous tissue disorder

Common: Ecchymosis

Uncommon: Rash

General disorders and administration site conditions

Uncommon: Fatigue

Glabellar Lines

Safety data were compiled from two double-blind, placebo-controlled, multicenter studies involving 405 patients treated with BOTOX®. The following adverse events were reported:

Nervous system disorders

Common: Headache, paresthesia

Eye disorders

Common: Eyelid ptosis

Gastrointestinal disorders

Common: Nausea

Skin and subcutaneous tissue disorders

Common: Erythema, skin tightness

Musculoskeletal and connective tissue disorders

Common: Muscular weakness

General disorders and administration site conditions

Common: Facial pain, injection site edema, ecchymosis, injection site pain, injection site irritation

The following adverse reaction in double-blind, placebo-controlled clinical studies within 90 days following injection of BOTOX® 24 Units for crow's feet lines alone was reported:

Crow's Feet Lines

Eye disorders

Common:Eyelid edema

There were no adverse drug reactions reported with the simultaneous treatment of crow's feet lines and glabellar lines at 44 Units.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type. A may reduce the effectiveness of **BOTOX®** treatment by inactivating the biological activity of the toxin.

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

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

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to **BOTOX®** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of neutralizing activity to **BOTOX®** with the incidence of antibodies to other products may be misleading.

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

Post-Marketing Experience

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.

Lagophthalmos has been reported following BOTOX® injection into the glabellar lines or crow's feet lines.

Eyelid edema has been reported following periocular BOTOX® injection.

The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in (Warnings and Precautions), and (Adverse Reactions): 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; rash; erythema multiforme; pruritus; dermatitis psoriasiform; hyperhidrosis; and alopecia, including madarosis dry eye, and localized muscle twitching/involuntary muscle contractions.

The following adverse reactions have been identified during post-approval use of **BOTOX®**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; aspiration pneumonia; brachial plexopathy; denervation/muscle atrophy; diarrhea; dry mouth; dysarthria; dyspnea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; muscle weakness; myalgia; myasthenia gravis; nausea; paresthesia; peripheral neuropathy; pruritis; pyrexia; radiculopathy; respiratory depression and/or respiratory failure; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption); strabismus; syncope; tinnitus; vertigo; vision blurred; visual disturbances; and vomiting.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin.

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

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

Overdosage:

Excessive doses of **BOTOX®** (Botulinum Toxin Type A) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection.

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.

Dosage Forms and Strengths:

Single-use, sterile 50 Units, 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection.

Dosage and Administration

Instructions for Safe Use

The potency Units of **BOTOX®** (Botulinum Toxin Type A) for injection are specific to the preparation and assay method utilized.

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

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

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

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

Preparation and Dilution Technique

BOTOX® is supplied in single-use 100 Units and 200 Units per vial. Prior to injection, reconstitute each vacuum-dried vial of **BOTOX®** with sterile, non-preserved 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX®** with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX®** should be administered within 24 hours after reconstitution. During this time period, reconstituted **BOTOX®** should be stored in a refrigerator (2° to 8°C).

Table 21 Dilution Instructions for **BOTOX®** Vials (50 Units, 100 Units and 200 Units)**

Diluent* Added to 50 Unit Vial	**Resulting Dose Units per 0.1 mL**	**Diluent* Added to 100 Unit Vial**	**Resulting Dose Units per 0.1 mL**	**Diluent* Added to 200 Unit Vial**	**Resulting Dose Units per 0.1 mL**
1 mL	5 Units	1 mL	10 Units	1 mL	20 Units
2 mL	2.5 Units	2 mL	5 Units	2 mL	10 Units
4 mL	1.25 Units	4 mL	2.5 Units	4 mL	5 Units
		8 mL	1.25 Units	8 mL	2.5 Units
		10 mL	1 Unit	10 mL	2 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

**For Neurogenic Detrusor Overactivity see specific dilution instructions in the NDO section below

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

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

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

Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)

General

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

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

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder (OAB)

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

The recommended dose is 100 Units of **BOTOX®** , and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with 0.9% non-preserved saline solution . Dispose of any unused saline.

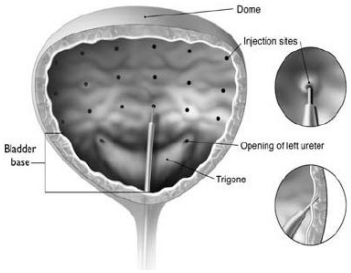
Reconstituted **BOTOX®** (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

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 8 below). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining **BOTOX®** in the needle is delivered to the bladder. After the injections are given, patients should demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

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

Figure 8: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Neurogenic Detrusor Overactivity



Neurogenic Detrusor Overactivity (NDO)

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

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

200 Unit Vial of BOTOX®

• Reconstitute a 200 Unit vial of **BOTOX®** with 6 mL of 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.

100 Unit Vial of BOTOX®

• 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 for a total of 4 mL in each 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.

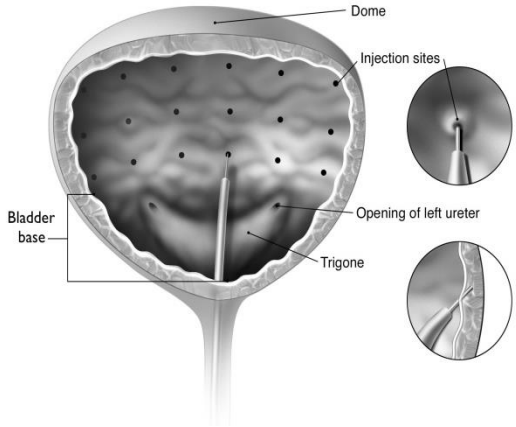
Reconstituted **BOTOX®** (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

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

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 8 below). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining **BOTOX®** in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

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

Figure 9:

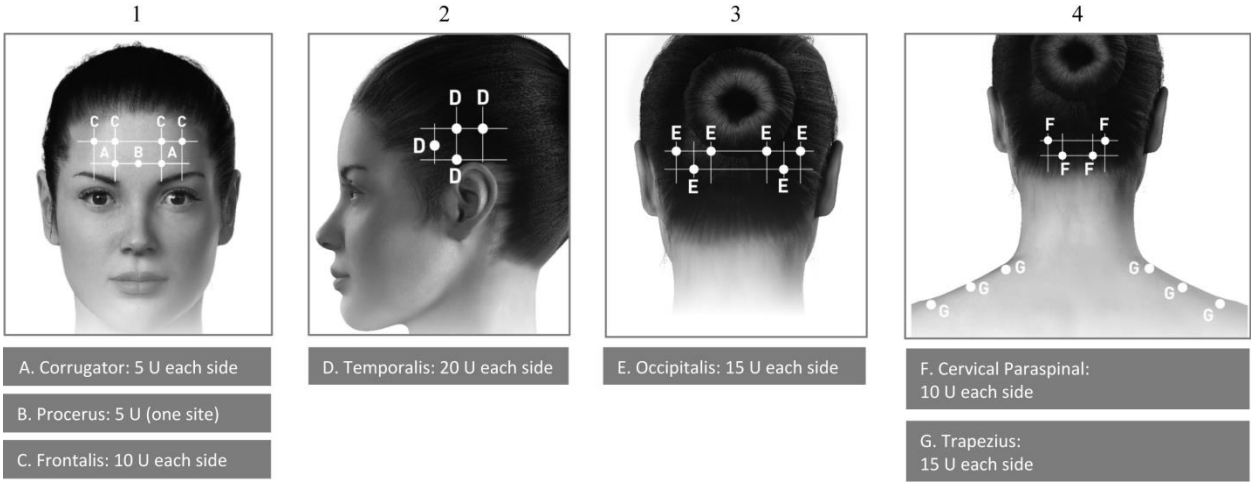


Chronic Migraine

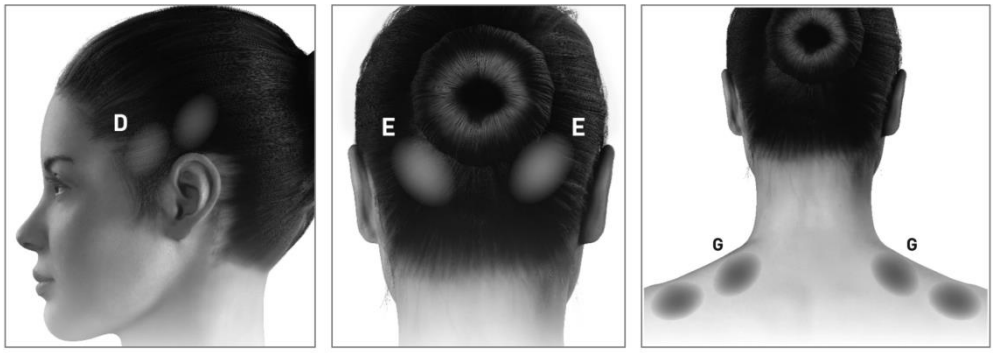
The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL. The recommended dose for treating chronic migraine is 155 Units administered intramuscularly using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections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

Recommended Injection sites (A thru G) for Chronic Migraine.

Figure 10:



5 6 7



D. Temporalis: 5 U/site (≤2 additional sites)

E. Occipitalis: 5 U/site (≤2 additional sites)

G. Trapezius: 5 U/site (≤4 additional sites)

1

Table 22: **BOTOX®** Dosing by Muscle for Chronic Migraine

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

[a] Each IM injection site = 0.1 mL = 5 Units **BOTOX®**

[b] Dose distributed bilaterally

Cervical Dystonia

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

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

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with 0.9% non-preserved sterile saline, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 21). In general, no more than 50 Units per site should be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles,

and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance may be useful.

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

Hyperhidrosis

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

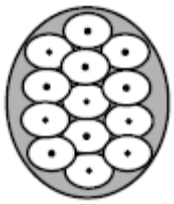
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine-Starch Test Procedure:

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

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

Figure 11: Injection Pattern for Hyperhidrosis



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

Blepharospasm

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

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

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

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

Hemifacial Spasm

Patients with hemifacial spasm or VII nerve disorder should be treated as for unilateral blepharospasm.

Further injections may be necessary into the corrugator, zygomaticus major, orbicularis oris and/or other facial muscles according to the extent of spasm.

Electromyographical control may be useful to identify small circumoral muscles. The cumulative dose of **BOTOX®** in a two month period should not exceed 200 U.

Spasticity (due to juvenile cerebral palsy)

Identification of treatment goals and the specific muscles responsible for the limiting pattern of spasticity must be undertaken prior to the injection of BOTOX®. In treating pediatric patients, the maximum cumulative dose in a 3 month interval should generally not exceed 8.0 Units/kg body weight or 300 Units, whichever is lower.

In clinical trials for the treatment of upper limb spasticity, the dose per muscle ranged from 0.5 to 2.0 Units/kg body weight in the upper limb per treatment session. The total dose ranged from 3.0 to 8.0 Units/kg body weight and did not exceed 300 Units divided among selected muscles at any treatment session.

In clinical trials for the treatment of equines foot deformity, the dose per muscle ranged from 2.0 to 4.0 Units/kg body weight in the lower limb per treatment session. The total dose was 4 Units/kg body weight or 200 Units (whichever was the lesser amount) divided among 1-2 sites in the medial and lateral gastrocnemius muscle of one or both legs at any treatment session. Following initial injection to the gastrocnemius muscle, further involvement of the anterior or posterior tibialis may need to be considered for additional improvement in the foot position at heel strike and during standing.

The table no 23 is intended to give dosing guidelines for injection of BOTOX® in the treatment of focal spasticity in children aged 2 years and older.

Table No 23:

Muscles in Upper Limb	**Dosage in Units/kg/muscle**	**Number of injections per muscle**
Biceps brachii	0.5 - 2.0	2-4 sites
Brachialis	0.5 - 2.0	1-2 sites
Brachioradialis	0.5 - 2.0	1-2 sites
Flexor carpi ulnaris	0.5 - 2.0	1-2 sites
Flexor carpi radialis	0.5 - 2.0	1-2 sites
Pronator teres	0.5 - 2.0	1-2 sites
Pronator quadratus	0.5 - 2.0	1-2 sites
Flexor digitorum profundus	0.5 - 2.0	1 site
Flexor digitorum sublimis	0.5 - 2.0	1 site
Flexor pollicis longus	0.5- 2.0	1 site
Flexor pollicis brevis	0.5 - 2.0	1 site

Opponens pollicis	0.5 - 2.0	1 site
Adductor pollicis	0.5 - 2.0	1 site

Muscles in Lower Limb	**Dosage in Units/kg/muscle**	**Number of injections per muscle**
Hip adductors (adductor longus, adductor brevis, adductor magnus, medial hamstrings)	4.0	2 sites
Gastrocnemius		
Medial	2.0	1-2 sites
Lateral	2.0	1-2 sites

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 typically not more frequently than every three months. The degree of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX® and muscles to be injected.

Spasticity (in adult post-stroke patients)

Upper Limb
In controlled and open label clinical trials the following doses for individual muscles were utilized up to a total dose of 400 Units per treatment session:

Table no 24

Muscle	**Total Dosage; Number of Sites**
Biceps brachii	100 – 200 Units; 1 to 4 sites
Flexor digitorum profundus	15 – 50 Units; 1-2 sites
Flexor digitorum sublimis	15 – 50 Units; 1-2 sites
Flexor carpi radialis	15 – 60 Units ; 1-2 sites
Flexor carpi ulnaris	10 – 50 Units; 1-2 sites
Adductor Pollicis	20 Units; 1-2 sites
Flexor Pollicis Longus	20 Units; 1-2 sites

In controlled and open, non-controlled clinical trials, doses usually between 200 and 240 Units in wrist and flexor muscles were divided among selected muscles at a given treatment session.

In controlled clinical trials, 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 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 generally not occur before 12 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of **BOTOX®** and muscles to be injected. The lowest effective dose should be used.

Lower Limb

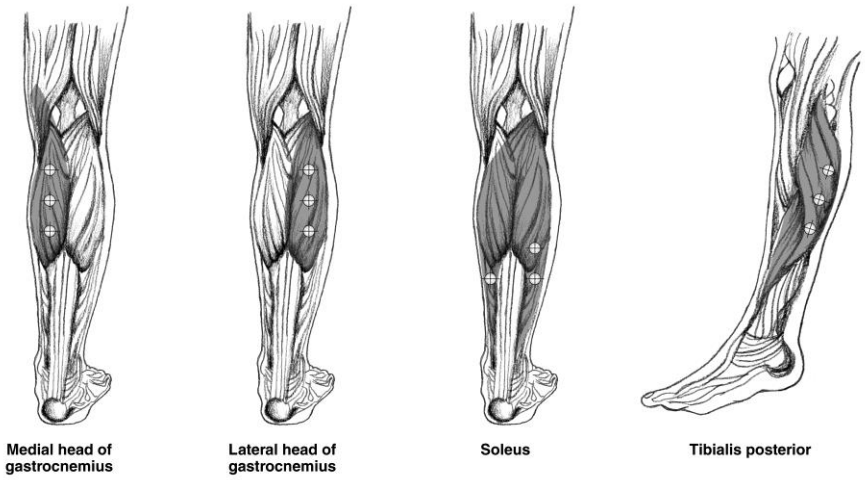
The recommended dose for treating adult lower limb spasticity involving the ankle is 300 Units divided among 3 muscles (see Table No 21 and Figure 12 below).

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 no 25: BOTOX® Dosing by Muscle for Adult Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage; Number of Sites
Gastrocnemius Medial head Lateral head	 75 Units; 3 sites 75 Units; 3 sites
Soleus	75 Units; 3 sites
Tibialis Posterior	75 Units; 3 sites

Figure 12: Injection Sites for Adult Lower Limb Spasticity



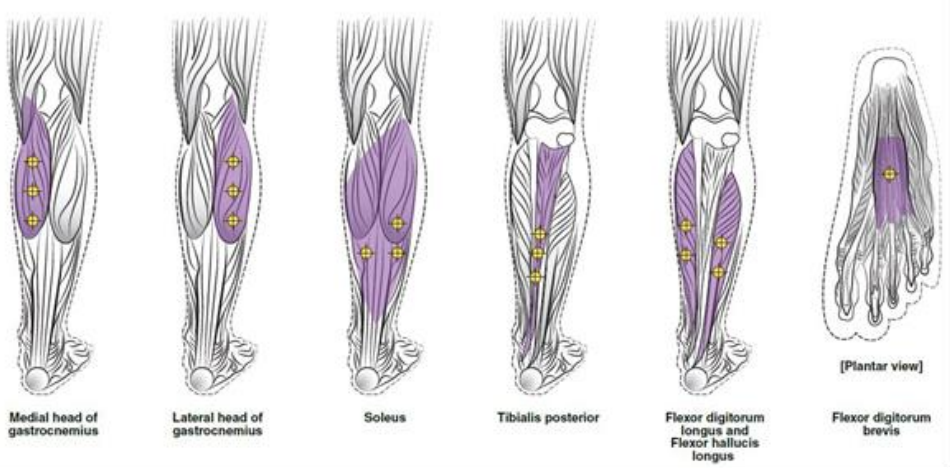
The recommended dose for treating adult lower limb spasticity involving the ankle and toes is 300 Units to 400 Units divided among affected muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, flexor digitorum longus and flexor digitorum brevis)

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. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of **BOTOX®** and muscles to be injected.

Table 26: BOTOX® Dosing by Muscle for Adult Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage; Number of Sites
Gastrocnemius Medial head Lateral head	 75 Units; 3 sites 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 13: Injection Sites for Adult Lower Limb Spasticity



Glabellar Lines

Using a 30-33 gauge needle, inject a dose of 0.1 mL (4 Units) intramuscularly into each of 5 sites (see Figure 14 below), 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units .Typically the initial doses of reconstituted **BOTOX®** induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

The duration of effect of **BOTOX®** for glabellar lines is approximately 3-4 months. The safety and effectiveness of more frequent dosing with **BOTOX®** has not been clinically evaluated and is not recommended.

Figure 14:

Crow's Feet Lines Injection technique:

Injections for Crow's Feet Lines should be given with the needle tip bevel up and oriented away from the eye. Using a 30-33 gauge needle, inject 4 Units/0.1 mL of reconstituted BOTOX® into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection (A) should be made at approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow's feet region are above and below the lateral canthus, inject per Figure 15. Alternatively, if the lines in the crow's feet region are primarily below the lateral canthus, inject per Figure 16.

Figure 15:

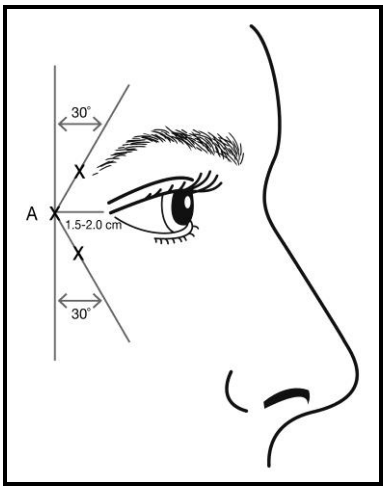
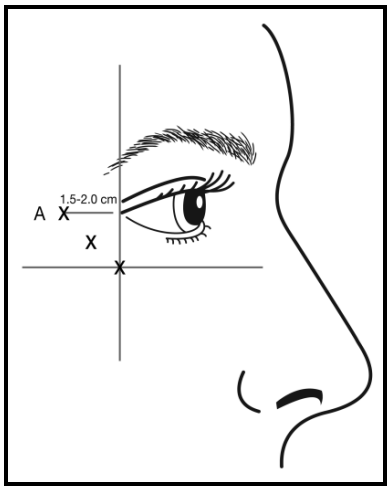


Figure 16:



For simultaneous treatment with glabellar lines, the dose is 24 Units for crow's feet lines and 20 Units for glabellar lines with a total dose of 44 Units.

The median time to onset of crow's feet lines treatment effect is three to four days. The duration of response with **BOTOX®** for crow's feet lines is up to 5 months. The safety and effectiveness of dosing with BOTOX® more frequently than every 3 months have not been evaluated

In treating adult patients for one or more indications with **BOTOX®**, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

The safe and effective use of **BOTOX®** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX®** must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures.

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected.

In order to reduce the complication of ptosis the following steps should be taken:

• Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.

• Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

• Ensure the injected volume/dose is accurate and where feasible kept to a minimum.

• Do not inject toxin closer than 1 cm above the central eyebrow.

Draw at least 0.5 mL of the properly reconstituted toxin into the sterile syringe, preferably a tuberculin syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-33 gauge needle. Confirm the patency of the needle. Inject a dose of 0.1 mL (4 Units) intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units.

How Supplied:

BOTOX® is supplied in a single use vial in 200 U or 100 U or 50 U.

Rx Only

Single use vial.

Storage:

Unopened vials of **BOTOX®** should be stored in a refrigerator (2˚ to 8˚ C) for up to 36 months for the 100 Units vials or up to 24 months for the 200 Units vial. Do not use after the expiration date on the vial. Administer **BOTOX®** within 24 hours of reconstitution; during this period reconstituted **BOTOX®** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX®** should be clear, colorless and free of particulate matter.

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