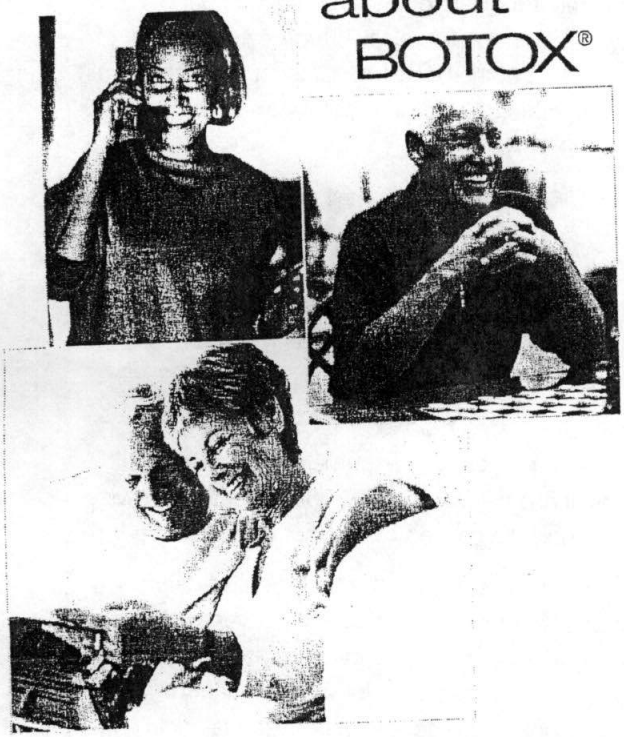
ANSWERS TO YOUR QUESTIONS about BOTOX®



BOTOX®
Botulinum Toxin Type A
Restoring form and function

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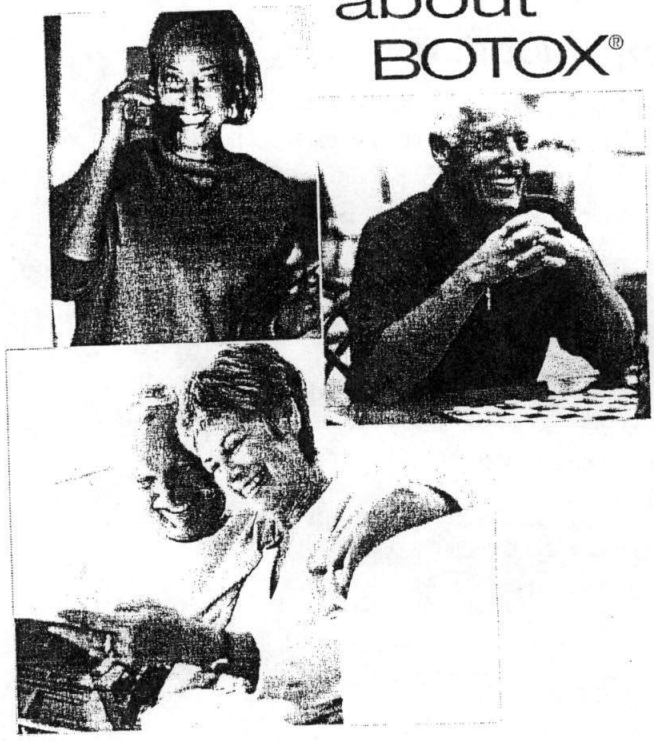

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Introduction

BOTOX® belongs to a class of drugs called botulinum toxins. BOTOX®, a focal muscle-relaxing agent, is the brand of botulinum toxin type A made by Allergan.

BOTOX® is the most studied brand of botulinum toxins and has been used to treat over 900,000 patients worldwide for more than 11 years.

This booklet is designed to help you understand the way BOTOX® works, its effectiveness and side effects. The potential of BOTOX® for continued use is also discussed.

You may find it helpful to keep this brochure for future reference.

QUESTION.
What is BOTOX®?

ANSWER.
BOTOX® is a formulation of botulinum toxin type A. It is derived from the bacterium *Clostridium botulinum.* This bacterium produces a protein that blocks the release of acetylcholine and relaxes muscles. Type A is just one of seven different types of botulinum toxin (A, B, C_1, D, E, F, and G), and each has different properties and actions. No two of these botulinum toxins are alike.

More than 100 years of research have expanded our knowledge of botulinum toxin type A from the identification of the bacterium *Clostridium botulinum* to the commercialization of botulinum toxin type A as BOTOX®.

In the 1960s, the muscle-relaxing properties of botulinum toxin type A were tapped for investigational use in realigning crossed eyes. These early studies paved the way for treating other conditions caused by overactive muscles with botulinum toxin type A.

Today, BOTOX® is produced in controlled laboratory conditions and given in extremely small therapeutic doses. It has helped over 900,000 patients worldwide with conditions caused by overactive muscles.

BOTOX® is indicated for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and associated neck pain. BOTOX® is also indicated for the treatment of blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in people 12 years of age and above.

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QUESTION.
Is BOTOX® a new treatment?

ANSWER.

No. BOTOX® has been used for more than 11 years to treat over 900,000 patients worldwide, and it is approved by the health ministries of at least 70 countries. BOTOX® has also been endorsed by the National Institutes of Health since 1990.[1]

QUESTION.
How is BOTOX® different from other botulinum toxin treatments?

ANSWER.

BOTOX® is Allergan's brand of botulinum toxin type A. A brand of botulinum toxin type B is also now available. The two toxins are different in several ways:

- They are different serotypes
- They have different manufacturing processes
- They work differently
- They require different doses

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QUESTION.
How is BOTOX® different from oral treatments?

ANSWER.

BOTOX® differs from oral therapies in that it is a non-systemic, focal therapy.

When drugs are taken orally, they are distributed throughout the body by the blood system. The drugs reach not only their desired site of action but also many additional sites. In contrast, BOTOX® is administered directly into the desired site of action. BOTOX® is not expected to be present in the blood stream at measurable levels following injection at the recommended doses.

QUESTION.
Why should you have confidence in BOTOX® ?

ANSWER.

BOTOX® provides targeted relief of symptoms for the treatment of neck pain and abnormal head position in Cervical Dystonia with

- No GI upset
- No fatigue
- No confusion
- No depression
- No liver toxicity

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BOTOX® has been proven as a safe and effective therapy, and has been widely used for more than 11 years.

Over the past 20 years, BOTOX® has been evaluated in more than 200 studies specific to approved indications in the US. Currently, little clinical data are published about botulinum toxin type B.

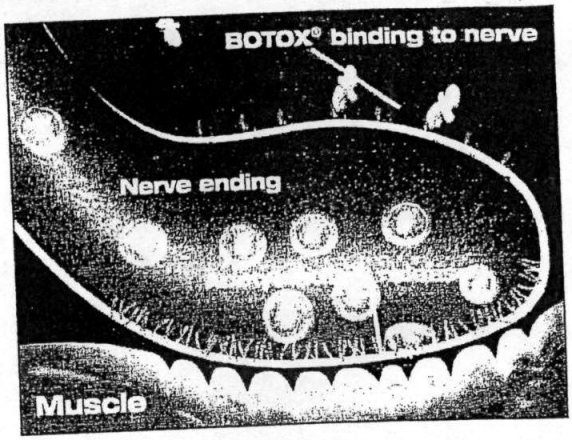
QUESTION.
How does BOTOX® work?

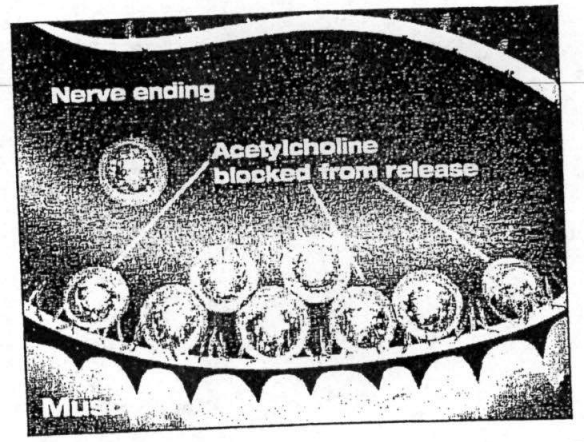
ANSWER.

Normally, your brain sends electrochemical messages to your muscles to make them contract and move. These messages are transmitted from a nerve to the muscle by a substance called acetylcholine. When too much acetylcholine is released, muscles become overly active and spasm or tense up.

BOTOX® blocks the nerve from releasing acetylcholine. As a result, the muscle spasms stop or are greatly reduced, providing relief from symptoms. Your health care provider will know how much BOTOX® is needed to treat you effectively.

It's important to remember that botulinum toxin treatment is not a cure. For many people, however, its effects have been dramatic. With BOTOX®, the nerve will take about 3 months to recover and begin to release acetylcholine, and the muscles may become overactive again. At that point, another injection will be needed to provide relief, as long as no allergic reactions or other significant side effects occurred and clinical response was obtained.





QUESTION.
How long can I be treated with BOTOX®?

ANSWER.

Each treatment typically lasts 3 months and can be repeated as long as your condition responds to BOTOX® and you do not have any serious allergic

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reactions or other significant side effects. BOTOX® has been used for more than 11 years to treat more than 900,000 patients worldwide, and although formal, long-term clinical evaluations have not been conducted, its safety in long-term use has been well established.

Although most people continue to respond to BOTOX® injections, some people have experienced a diminished response over time. There may be several explanations for this:

1. **Changes in your condition**—If the pattern of your muscle activity changes, your health care provider may need to inject new muscles and/or change your dose. Identifying and injecting the affected muscle can be difficult, complicated by the changing pattern of muscle involvement and progression of the disorder.
2. **Setting appropriate expectations**—You may believe your first BOTOX® injection was more helpful than subsequent injections. That's because your condition was perhaps quite severe when you had your first injection. Subsequent injections are usually given before your condition becomes that severe again. Therefore, the relief you experienced with subsequent injections may not have been as dramatic as the first time.
3. **Antibody formation**—When foreign proteins, like botulinum toxins, enter your body, antibodies may form. If antibodies to botulinum toxin develop, you may no longer respond to treatment.

Because botulinum toxins are usually used to treat chronic conditions, it's important to preserve responsiveness to therapy.

QUESTION.

How can I help maintain my response to BOTOX®?

ANSWER.

While the critical factors for neutralizing antibody formation have not been well characterized, you may be able to help maintain your response to BOTOX® by minimizing your total exposure. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

QUESTION.

How is BOTOX® given?

ANSWER.

BOTOX® is injected into the affected muscle(s). Your doctor will determine which muscles need to be treated.

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QUESTION.
Does the injection hurt?

ANSWER.

Some people report minor, temporary discomfort from the injection. BOTOX® is reconstituted with sterile, preservative-free, normal saline for injection. The neutral pH of the injected solution, in combination with the fine-gauge needle your doctor will use, can help to minimize any injection-related pain.

QUESTION.
When will BOTOX® start to work?

ANSWER.

If you're receiving BOTOX® for cervical dystonia, you'll usually see the effects within 2 weeks of the injection. If you're receiving BOTOX® for blepharospasm, you'll usually see effects within 3 days.

QUESTION.
How long will the effect last?

ANSWER.

BOTOX® offers sustained relief, dose after dose. The relief you'll feel from one treatment of BOTOX® will normally last for about 3 months. Treatments can be continued as long as your condition responds to BOTOX®, and you do not have any serious allergic reactions or other significant side effects. When the relief begins to fade, you'll return to your doctor for your next treatment.

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Usually, BOTOX® treatment is required approximately four times per year. Because symptoms can change over time, the amount and duration of relief you'll experience can vary. Consult your doctor, who can determine how to achieve the best possible results with BOTOX®.

QUESTION.
What side effects have been seen with BOTOX®?

ANSWER.

The most frequently reported adverse reactions in patients receiving BOTOX® for the treatment of cervical dystonia are dysphagia (difficulty swallowing, 19%), upper respiratory infection (such as a cold or flu,12%), neck pain (11%), and headache (11%). Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients. In these patients, there are reports of rare cases of dysphagia serious enough to require the insertion of a gastric feeding tube (a tube for introducing nutritious, high-calorie fluids into the stomach.)

The most frequently reported treatment-related adverse reactions in patients receiving BOTOX® for the treatment of blepharospasm are ptosis (droopy eyelids, 20.8%), superficial punctuate keratitis (inflammation of the cornea characterized by small erosions of the tissue covering the cornea, 6.3%), and eye dryness (6.3%). Reduced blinking from

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BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect (a defect in the corneal covering) and corneal ulceration (a hollowed-out cavity in the cornea), especially in patients with VII nerve disorders.

In general, adverse reactions occur within the first week following injection of BOTOX® and, while generally transient, may last several months. Localized pain, tenderness and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

Please seek immediate medical attention if swallowing, speech, or respiratory (breathing) disorders arise.

QUESTION.

Is BOTOX® right for me?

ANSWER.

Your health care provider can help you decide if BOTOX® is right for you. In order to make the right treatment decision, you should discuss the following with your health care provider before choosing treatment:

- Clinical experience with the drug
- Effectiveness and side effects

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Make sure your health care provider knows if you are pregnant, nursing, or taking any medications before receiving BOTOX® injections. Additionally, you should not receive BOTOX® if you have an infection at the injection site.

BOTOX® should be used with caution if you have other neurological diseases or disorders, or if you are taking aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission. Be sure to tell your health care provider about any prescription or over-the-counter medications you are taking before receiving BOTOX®.

QUESTION.

How can I find out if my insurance covers BOTOX®?

ANSWER.

The BOTOX ADVANTAGE™ Program Reimbursement Hotline has been helping patients and physicians get answers to their BOTOX® reimbursement questions for years. In addition, BOTOX® has more than a decade of reimbursement experience with insurance carriers and health care providers. It is this experience that has resulted in BOTOX® coverage by most payers, including Medicare and Medicaid; particularly for cervical dystonia.

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Some insurance plans cover BOTOX® under the medical benefit and others cover BOTOX® under the pharmacy benefit. To find out how BOTOX® is covered under your insurance plan, call the BOTOX ADVANTAGE™ Program Reimbursement Hotline, toll-free, at **1-800-530-6680**. Our knowledgeable Hotline staff is available to assist you with your insurance coverage questions Monday through Friday from 8:00 AM to 6:00 PM ET.

Additionally, Hotline representatives will help physicians and patients research alternative coverage for those who do not have insurance or cannot qualify for government assistance. If the Hotline representatives cannot find alternative coverage, they will help determine if patients meet the criteria for the BOTOX® Patient Assistance Program. The BOTOX® Patient Assistance Program is available to all patients who lack insurance coverage and demonstrate financial need.

QUESTION.

Where can I learn more about blepharospasm and cervical dystonia?

ANSWER.

Your health care provider is the best source of information about your condition and its treatment. However, there are several organizations that you may also find helpful:

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Benign Essential Blepharospasm Research Foundation (BEBRF)
(409) 832-0788
www.blepharospasm.org

Dystonia Medical Research Foundation (DMRF)
(312) 755-0198 • (800) 377-DYST
www.dystonia-foundation.org

ST/Dystonia, Inc.
(262) 560-9534 • (888) 445-4588
www.spasmodictorticollis.org

The National Spasmodic Torticollis Association (NSTA)
(714) 378-7837 • (800) 487-8385
www.torticollis.org

WE MOVE—Worldwide Education and Awareness for Movement Disorders
(800) 437-MOV2
www.wemove.org

For more information on BOTOX®
Contact us at our website:
www.BOTOX.com
or call **1-800-44-BOTOX**

References:

1. US Dept of Health and Human Services. *Botulinum Toxin. Consensus Statement.* NIH Consensus Development Conference; November 12-14, 1990. Bethesda, Md: National Institutes of Health; 1990.

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BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex

Manufactured by:
Allergan Pharmaceuticals Ireland
a subsidiary of:
Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612

Description: **BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex** is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin (Human) and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One unit (U) of **BOTOX®** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to Allergan's product, **BOTOX®**. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, 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. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of **BOTOX®** is approximately 20 units/nanogram of neurotoxin protein complex.

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

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

Pharmacokinetics

Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels following IM 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, sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.

Clinical Studies:

Cervical dystonia:

A phase 3 randomized, multi-center, double blind, placebo-controlled study of the treatment of cervical dystonia was conducted.[1] 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 in Table 1.

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]
Percentage Patients with Any Improvement on Physicians 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 (see also Precautions: Geriatrics). There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

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

In the phase 3 study the median total **BOTOX®** dose in patients randomized to receive **BOTOX®** (n=88) was 236 U, 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 in Table 2. 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.

NOTE: There were 16 patients who had additional muscles injected.

Blepharospasm:

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label uncontrolled study, 27 patients with essential blepharospasm were injected with 2.0 U of **BOTOX®** at each of six sites on each side. One patient had not received any prior treatment. Twenty-six of the patients had not responded to therapy with benztropine mesylate, clonazepam and/or baclofen. Three of the 26 patients continued to experience spasms following muscle stripping surgery. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.[2]

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.[3]

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12.5 weeks prior to the need for re-treatment.[4]

In general, adverse events occur within the first week following injection of **BOTOX®** and while generally transient may have a duration of several months. Localized pain, tenderness and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

Cervical Dystonia:
In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of **BOTOX®**, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).[7]

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported rarely.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of **BOTOX®** resulting from the spread of the toxin outside the injected muscles.

The most common severe adverse event associated with the use of **BOTOX®** injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea. (See Warnings). Most dysphagia is reported as mild or moderate in severity. However, it may rarely be associated with more severe signs and symptoms (See Warnings).

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

Blepharospasm:
In a study of blepharospasm patients who received an average dose per eye of 33 U (injected at 3 to 5 sites) of the currently manufactured **BOTOX®**, the most frequently reported treatment-related adverse reactions were ptosis (20.8%), superficial punctate keratitis (6.3%) and eye dryness (6.3%).[8]

In this study, the rate for ptosis in the current **BOTOX®** treated group (20.8% of patients) was significantly higher than the original **BOTOX®** treated group (4.0% of patients) (p=0.014%). All of these events were mild or moderate except for one case of ptosis which was rated severe.

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

In two cases of VII nerve disorder (one case of an aphakic eye), reduced blinking from **BOTOX®** injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and corneal ulceration. Perforation occurred in the aphakic eye and required corneal grafting.

A report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus:
Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviation, especially with higher doses of **BOTOX®**. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus are 15.7% and 16.9%, respectively.[4]

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

The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection.

Ptosis (0.3%) and vertical deviation greater than two prism diopters (2.1%) were reported to persist for over six months in a larger series of 5587 injections of horizontal muscles in 3104 patients.

In these patients, the injection procedure itself caused nine scleral perforations. A vitreous hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar hemorrhages occurred without visual loss. Decompression of the orbit after five minutes was done to restore retinal circulation in one case. Five eyes had pupillary change consistent with ciliary ganglion damage (Adie's pupil).

One patient developed anterior segment ischemia after receiving **BOTOX®** injection into the medial rectus muscle under direct visualization for esotropia.

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. The rate of formation of neutralizing antibodies in patients receiving **BOTOX®** has not been well studied.

In the phase 3 cervical dystonia study[1] that enrolled only patients with a history of receiving **BOTOX®** for multiple treatment sessions, at study entry there were 192 patients with antibody assay results, of whom 33 (17%) had a positive assay for neutralizing activity. There were 96 patients in the randomized period of the phase 3 study with valid assays at both study entry and end and who were neutralizing activity negative at entry. Of these 96, 2 patients (2%) converted to positive for neutralizing activity. Both of these converting patients were among the 52 who had received two **BOTOX®** treatments between the two assays; none were in the group randomized to placebo in the controlled comparison period of the study.

In the randomized period of the phase 3 study, patients in the **BOTOX®** group whose baseline assays were neutralizing antibody negative showed improvements on CDSS (n=64, mean CDSS change -2.1) while patients whose baseline assays were neutralizing antibody positive did not (n=14, mean CDSS change +1.1). However, in uncontrolled studies there are also individual patients who are perceived as continuing to respond to treatments despite the presence of neutralizing activity. Not all patients who become non-responsive to **BOTOX®** after an initial period of clinical response have demonstrable levels of neutralizing activity.

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 neutralizing activity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of neutralizing activity to **BOTOX®** with the incidence reported 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.

Overdosage:
Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis.

An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. In the event of an overdose or injection into the wrong muscle, immediately contact Allergan for additional information at (800) 433-8871 from 8:00 a.m. to 4:00 p.m. Pacific Time, or at (714) 246-5954 for a recorded message at other times. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

Dosage and Administration:
BOTOX® is supplied in a single use vial. Because the product and diluent do not contain a preservative, once opened and reconstituted, store in a refrigerator and use within four hours. Discard any remaining solution. Do not freeze reconstituted **BOTOX®**.

BOTOX® is to be reconstituted with sterile, non-preserved saline prior to intramuscular injection.

General:
An injection of **BOTOX®** is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin (see Dilution Table) 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®**.

The method utilized for performing the potency assay is specific to Allergan's Botulinum Toxin Type A. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various potency assays, Units of biological activity of Botulinum Toxin Type A cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal dose-activity relationships to human dose relationships.

Cervical dystonia:
The phase 3 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 the phase 3 study was 236 U (25th to 75th percentile range 198 U to 300 U). The **BOTOX®** dose was divided among the affected muscles (see Clinical Studies: Cervical Dystonia). 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 muscles to 100 U or less may decrease the occurrence of dysphagia (see Precautions: Cervical Dystonia).

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