BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex

Manufactured by: Allergan Pharmaceuticals Ireland
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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 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 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. When injected intramuscularly at therapeutic doses, **BOTOX®** produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by **BOTOX®**.

When injected intradermally, **BOTOX®** produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Pharmacokinetics

Botulinum Toxin Type A is not expected to be present 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, 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 Units, with 25th to 75th percentile ranges of 198 to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 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.

Primary Axillary Hyperhidrosis:

The efficacy and safety of **BOTOX®** for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies.

Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1= "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities." A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of **BOTOX®**, 75 Units of **BOTOX®**, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

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

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

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both **BOTOX®** groups than in the placebo group ($p < 0.001$), but was not significantly different between the 2 **BOTOX®** doses (See Table 3).

Table 3: Study 1 - Study Outcomes

Treatment Response	BOTOX® 50 Units N = 104	BOTOX® 75 Units N=110	Placebo N= 108	BOTOX® 50-placebo (95% CI)	BOTOX® 75-placebo (95% CI)
HDSS Score change ≥2 % (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production %(n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

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

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in **BOTOX®**-treated patients with either dose was 201 days. Among those who received a second **BOTOX®** injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either

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

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 Units 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]

Strabismus:
It is postulated that when used for the treatment of strabismus, the administration of **BOTOX®** effects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the muscle's antagonist; it was on the basis of this hypothesis that clinical studies were conducted. Six hundred seventy-seven patients with strabismus treated with one or more injections of **BOTOX®** were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.[5] These results are consistent with results from additional open label trials which were conducted for this indication.[4]

INDICATIONS AND USAGE:
BOTOX® is indicated for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia.

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

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

The efficacy of **BOTOX®** treatment in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been established. **BOTOX®** is ineffective in chronic paralytic strabismus except when used in conjunction with surgical repair to reduce antagonist contracture.

CONTRAINDICATIONS:
BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS:
The recommended dosage and frequency of administration for **BOTOX®** should not be exceeded. Risks resulting from administration at higher dosages are not known.

Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. 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. If such a reaction occurs further injection of **BOTOX®** should be discontinued and appropriate medical therapy immediately instituted.

Pre-Existing Neuromuscular Disorders
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) should only receive **BOTOX®** with caution. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX®**. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular 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.

Dysphagia
Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

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

PRECAUTIONS:
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 may be useful for the treatment of cervical dystonia.

Caution should be used 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).

Cervical Dystonia:
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.

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

The safety and effectiveness of **BOTOX®** for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive **BOTOX®** for palmar hyperhidrosis and facial hyperhidrosis, respectively.

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

Strabismus:
During the administration of **BOTOX®** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Information for Patients:
Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech or respiratory disorders arise.

Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia, which is typically mild to moderate, but could be severe. Rare consequences of severe dysphagia include aspiration, dyspnea, pneumonia, and the need to reestablish an airway.

As with any treatment with the potential to allow previously sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually following the administration of **BOTOX®**.

Drug Interactions:
Co-administration of **BOTOX®** and aminoglycosides[6] or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes 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.

Pregnancy: **Pregnancy Category C**
When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL of **BOTOX®** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification which may be reversible.

In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX®**.

There are no adequate and well-controlled studies of **BOTOX®** in pregnant women. Because animal reproductive studies are not always predictive of human response, **BOTOX®** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations which have been observed in rabbits.

Carcinogenesis, Mutagenesis, Impairment of fertility: Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX®**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos.

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

Pediatric use: Safety and effectiveness in children below the age of 12 have not been established for blepharospasm or strabismus, or below the age of 16 for cervical dystonia or 18 for hyperhidrosis.

Geriatric use: Clinical studies of **BOTOX®** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general,

dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

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

The following events have been reported since the drug has been marketed and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

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 Units of **BOTOX®** for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis:
The most frequently reported adverse events (3-10% of patients) following injection of **BOTOX®** in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

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BOTOX®

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

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

Blepharospasm:
In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured **BOTOX®**, the most frequently reported 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 cervical dystonia 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.

One patient among the 445 hyperidrosis patients with analyzed specimens showed 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 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 Units (25th to 75th percentile range 198 Units to 300 Units). 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 Units 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.

Clinical improvement generally begins within the first two weeks after injection with maximum

clinical benefit at approximately six weeks post-injection. In the phase 3 study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

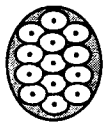
Primary Axillary Hyperhidrosis:
The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. **BOTOX®** is reconstituted with 0.9% non-preserved sterile saline (100 Units/4 mL). Using a 30 gauge 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, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 1:

Figure 1:



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

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 5.0 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, but it is rare to have the effect be permanent.

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

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

To prepare the eye for **BOTOX®** injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

Note: The volume of **BOTOX®** injected for treatment of strabismus should be between 0.05 - 0.15 mL per muscle.

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

I. Initial doses in Units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

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

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

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

II. Subsequent doses for residual or recurrent strabismus.

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

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

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

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

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

Dilution Technique:
Prior to injection, reconstitute vacuum-dried **BOTOX®**, with sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe, 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 four hours after reconstitution.

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

Dilution Table

Diluent Added (0.9% Sodium Chloride Injection)	**Resulting dose Units per 0.1 mL**
1.0 mL	10.0 Units
2.0 mL	5.0 Units
4.0 mL	2.5 Units
8.0 mL	1.25 Units

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.)

HOW SUPPLIED:
BOTOX® is supplied in a single use vial. Each vial contains 100 Units of vacuum-dried Clostridium botulinum type A neurotoxin complex. NDC 0023-1145-01.

Vials of **BOTOX®** have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or flourescent light source. (Note the holographic film on the label is absent in the date/batch area.) If you do not see the lines of rainbow color or the name "Allergan", do not use the product and contact Allergan for additional information at (800) 890-4345 from 8:00 a.m. to 4:00 p.m. Pacific time.

Rx Only

Single use vial.

Storage:
Unopened vials of **BOTOX®** should be stored in a refrigerator (2° to 8° C) for up to 24 months. Do not use after the expiration date on the vial. Administer **BOTOX®** within 4 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.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

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

U.S. Pat. 6,683,049

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