

ALLERGAN

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Dear Valued Customer,

You may have seen recent media coverage about BOTOX[®] Cosmetic (Botulinum Toxin Type A) and BOTOX[®]. Unfortunately many of the recent stories have misrepresented the facts surrounding BOTOX[®] Cosmetic, so we wanted to take an opportunity to share the attached fact sheets with you to answer any questions you or your patients may have.

If you have any additional concerns, please speak with your sales representative or contact Allergan's Medical Information Department at 1-800-433-8871.

Thank you,

Allergan, Inc.



BOTOX[®] Cosmetic and BOTOX[®] (Botulinum Toxin Type A) By the Numbers

- **3,181,592:** Number of BOTOX[®] Cosmetic treatments administered in the United States in 2006 aloneⁱ
- **1,000,000s:** People who received treatment with BOTOX[®] for medical and aesthetic purposes around the worldⁱⁱ
- **300,000:** Number of *men* who received treatment with BOTOX[®] Cosmetic in 2006ⁱⁱⁱ
- **10,000:** People in clinical trials^{iv}
- **3,000:** Publications on Botulinum Toxin Type A in scientific and medical journals^v
- **100:** Years of study into botulinum neurotoxins^{vi}
- **97:** Percentage of people satisfied with their BOTOX[®] Cosmetic treatment based on a survey of approximately 1,000 patients^{vii}
- **75:** Countries around the world who have approved use of BOTOX^{®viii}
- **20:** BOTOX[®] indications approved by regulatory authorities around the world^{ix}, including the aesthetic indication
- **18:** Years since U.S. Food and Drug Administration (FDA) approved BOTOX[®] to treat excessive eye blinking and crossed eyes^x
- **11:** Descriptor for the glabellar (vertical) lines between the brows which can be treated with BOTOX[®] Cosmetic, that can help improve one's overall facial appearance^{xi}
- **8:** Years since FDA approval of BOTOX[®] for the treatment of cervical dystonia (painful neck twisting condition) in adults^{xii}
- **6:** Years since FDA approval of BOTOX[®] Cosmetic for the treatment of the moderate to severe glabellar (vertical) lines between the brows^{xiii} in adults 18 to 65
- **4:** Years since FDA approval of BOTOX[®] for the treatment of severe primary hyperhidrosis^{xiv} (excessive underarm sweating) inadequately managed with topical agents
- **1:** Rank of BOTOX[®] Cosmetic on list of "Top 5 Surgical & Nonsurgical Physician Administered Cosmetic Procedures,"^{xv} according to American Society for Aesthetic Plastic Surgery

About BOTOX® (Botulinum Toxin Type A)

BOTOX® is a medical product that contains tiny amounts of highly purified botulinum toxin protein refined from a bacterium. The product is administered in small therapeutic doses by injection directly into the affected area, and works by blocking the release of acetylcholine (a neurotransmitter that signals the muscles to contract) at the neuromuscular junction.

BOTOX® neurotoxin therapy was granted approval by the FDA in 1989 for the treatment of strabismus (crossed eyes) and blepharospasm (uncontrollable eye blinking) 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.

BOTOX® neurotoxin has since received approval in December 2000 for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia. In 2002, with dosing specific to treat frown lines between the eyebrows, the product was approved by the FDA for the temporary improvement in the appearance of moderate to severe glabellar lines (the vertical "frown lines" between the eyebrows) in adult men and women aged 65 and younger, under the name BOTOX® Cosmetic. More recently, in July 2004, BOTOX® was granted FDA approval for the treatment of severe primary axillary hyperhidrosis (excessive underarm sweating) that is inadequately managed with topical agents.

Important Risk Information

BOTOX® and BOTOX® Cosmetic treatment should not be injected in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

Serious heart problems and serious allergic reactions have been reported rarely. If you think you're having an allergic reaction or other unusual symptoms, such as difficulty swallowing, speaking or breathing, call your doctor immediately. 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® or BOTOX® Cosmetic with caution. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic side effects with BOTOX® or BOTOX® Cosmetic.

BOTOX® for Blepharospasm in Patients \geq 12 Years of Age: Reduced blinking from BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal perforation. The most frequently reported treatment-related adverse reactions in these patients are ptosis (20.8%), superficial punctate keratitis (6.3%) and eye dryness (6.3%).

BOTOX® for Strabismus in Patients \geq 12 Years of Age: Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. The most commonly reported adverse effects are ptosis (16%) and vertical deviation (17%).

BOTOX® for Cervical Dystonia in Adults: There have been rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. The most frequently reported adverse reactions in patients with cervical dystonia are dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

BOTOX® for Severe Primary Axillary Hyperhidrosis Inadequately Managed with Topical Agents: The most frequently reported adverse events (3 - 10%) are injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

BOTOX[®] Cosmetic for Temporary Improvement in the Appearance of Moderate to Severe Frown Lines Between the Brows in adults ≤ 65 : The most common side effects following injection include temporary eyelid droop and nausea. Localized pain, infection, inflammation, tenderness, swelling, redness and/or bleeding/bruising may be associated with the injection.

For full prescribing information for BOTOX[®] and BOTOX[®] Cosmetic, please visit www.BOTOXMedical.com or www.BOTOXCosmetic.com.

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ⁱ American Society for Aesthetic Plastic Surgery Quick Facts <http://www.surgery.org/download/2006stats.pdf>

ⁱⁱ Allergan press release "Allergan, Inc Responds to Public Citizen's Allegation Regarding a Fatality Following BOTOX[®] Cosmetic Treatment" 01/25/08

ⁱⁱⁱ American Society for Aesthetic Plastic Surgery Quick Facts <http://www.surgery.org/download/2006stats.pdf>

^{iv} Allergan press release "Allergan, Inc Comments on BOTOX[®] (Botulinum Toxin Type A) Safety Profile" Released 01/24/08

^v BOTOX[®] History and Development Fact Sheet, updated 01.04.08

^{vi} BOTOX[®] History and Development Fact Sheet, updated 01.04.08

^{vii} Aesthetic Surgery Education & Research Foundation press release "First-of-its-kind Survey Finds That BOTOX Cosmetic has Gone Mainstream" Released 04/28/06

^{viii} BOTOX[®] Fact Sheet, updated 01.04.08

^{ix} BOTOX[®] Fact Sheet, updated 01.04.08

^x BOTOX[®] Fact Sheet, updated 01.04.08

^{xi} BOTOX[®] Fact Sheet, updated 01.04.08

^{xii} BOTOX[®] Fact Sheet, updated 01.04.08

^{xiii} BOTOX[®] Fact Sheet, updated 01.04.08

^{xiv} BOTOX[®] Fact Sheet, updated 01.04.08

^{xv} American Society for Aesthetic Plastic Surgery Top 5 Surgical & Nonsurgical Cosmetic Procedures <http://www.surgery.org/download/2006-Top5.pdf>



BOTOX[®] Cosmetic (Botulinum Toxin Type A) Fact Sheet

- More than 13 million aesthetic procedures with BOTOX[®] Cosmetic (botulinum toxin type A) have been administered since the product was first approved in 2002 in the United States for temporary treatment of moderate to severe glabellar lines (the vertical “frown lines” between the eyebrows) in adults 18 to 65.ⁱ
- According to the American Society for Aesthetic Plastic Surgery (ASAPS), more than three million BOTOX[®] Cosmetic treatments were administered in 2006 alone.ⁱⁱ
- Ninety-seven percent of patients were definitely satisfied with BOTOX[®] Cosmetic treatments, according to a survey of approximately 1,000 patients conducted by the research arm of ASAPS.ⁱⁱⁱ
- BOTOX[®] Cosmetic, approved for the temporary treatment of glabellar lines, is the same medicine that is used to treat patients with neurological conditions under the name BOTOX[®]. It is, however, administered in much smaller doses for aesthetic use. The approved doses of BOTOX[®] for medical uses are significantly greater than the approved dose for an aesthetic procedure.
- BOTOX[®] Cosmetic is a simple, minimally invasive injectable treatment that creates a temporary smoothed and improved appearance of the wrinkle-causing muscles between the brows that lasts up to four months. Most side effects are temporary and typically associated with the injection itself, such as localized pain, tenderness, redness and/or bruising. (See full safety information provided below).
- Since its first approval more than 18 years ago, reports of serious adverse events in patients receiving BOTOX[®] have been rare.
- BOTOX[®] Cosmetic should only be administered by a licensed health care professional who is well trained in the anatomy of the face.

About the FDA Safety Review of Botulinum Toxin Products in the United States:

- As you may know, the U.S. Food and Drug Administration (FDA) recently issued a news release regarding its ongoing safety review of botulinum toxin treatments in the United States, including BOTOX[®] and BOTOX[®] Cosmetic (botulinum toxin type A).
- As part of the FDA's ongoing commitment to safety evaluation and communication to the public, the Agency recently has adopted a routine protocol to provide an "early communication" regarding safety or other related reviews, often before any conclusions are or can be made. The FDA will communicate its conclusions and resulting recommendations after its review of the data has been completed.
- The FDA inquiry relates primarily to small number of high dose medical uses of BOTOX[®] that have occurred over the past 18 years, particularly for the management of juvenile cerebral palsy (JCP) and other large muscle, lower limb spasticities. Use of botulinum toxins for treatment of limb spasticity (severe arm and leg muscle spasms) in children or adults is not an approved use in the United States. The FDA indicated that this JCP population often consists of sick and compromised patients. The FDA also indicated that these reactions may relate to very high doses. By way of comparison, some of these adverse event reports, submitted promptly by Allergan to the FDA, indicated doses of greater than 20-100 times that of a typical aesthetic use on a per kilogram of body weight basis. However, the FDA will review certain adverse event reports for both unapproved and approved uses of BOTOX[®] and BOTOX[®] Cosmetic.
- Furthermore, it is important to understand that a report of an adverse event following treatment with BOTOX[®] and BOTOX[®] Cosmetic does not by itself mean that the drug caused the event, just that the event occurred after treatment with the drug so it needs to be investigated. The FDA is not advising HCPs to stop using BOTOX[®] Cosmetic.
- In its entire history, there has never been a single reported death where a causal link to BOTOX[®] Cosmetic was established.
- As the product labeling for BOTOX[®] Cosmetic already states, patients with pre-existing neuromuscular disorders may be at increased risk of clinically significant systemic effects from typical doses of BOTOX[®] Cosmetic. Patients should always consult with their physician to see if treatment with BOTOX[®] Cosmetic is right for them.

Important BOTOX[®] Cosmetic (Botulinum Toxin Type A) Information

BOTOX[®] Cosmetic is approved for the temporary treatment of moderate to severe frown lines between the brows in people 18 to 65 years of age.

BOTOX[®] Cosmetic is the only product of its type approved by the U.S. Food and Drug Administration for the treatment of moderate to severe frown lines between the brows. BOTOX[®] Cosmetic should only be administered by a trained and qualified health care provider.

Important BOTOX[®] Cosmetic Safety Information

Serious heart problems and serious allergic reactions have been reported rarely. If you think you're having an allergic reaction or other unusual symptoms, such as difficulty swallowing, speaking or breathing, call your doctor immediately. The most common side effects following injection include temporary eyelid droop and nausea. Localized pain, infection, inflammation, tenderness, swelling, redness and/or bleeding/bruising may be associated with the injection. Patients with certain neuromuscular disorders such as ALS, myasthenia gravis or Lambert-Eaton syndrome may be at increased risk of serious side effects.

For full prescribing information on BOTOX[®] Cosmetic, please visit www.BOTOXCosmetic.com

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ⁱ American Society for Aesthetic Plastic Surgery <http://www.surgery.org>

ⁱⁱ American Society for Aesthetic Plastic Surgery Quick Facts <http://www.surgery.org/download/2006stats.pdf>

ⁱⁱⁱ Aesthetic Surgery Education & Research Foundation press release "First-of-its-kind Survey Finds That BOTOX Cosmetic has Gone Mainstream" Released 04/28/06

BOTOX® COSMETIC
(Botulinum Toxin Type A)
Purified Neurotoxin Complex

Manufactured by:
Allergan Pharmaceuticals Ireland
A subsidiary of: **Allergan, Inc.**
2525 Dupont Dr.
Irvine, California 92612

DESCRIPTION

BOTOX® COSMETIC (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® COSMETIC** corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice. The method utilized for performing the assay is specific to Allergan's product **BOTOX® COSMETIC**. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD₅₀ assays, Units of biological activity of **BOTOX® COSMETIC** cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. In addition, 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® COSMETIC** is approximately 20 units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX® COSMETIC** 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® COSMETIC 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® COSMETIC** 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® COSMETIC**.

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. These side effects may be due to local spread of toxin from the injection site and/or misplaced injections.

Clinical studies have reported changes in clinical electromyographic parameters (i.e., jitter) in muscles distant to the site of **BOTOX®** injection. This may indicate spread of the toxin via circulation, retro- or ortho-grade axonal transport, or some action of the toxin at a third, central, or unidentified site.

CLINICAL STUDIES

Glabella Lines:

Two phase 3 randomized, multi-center, double blind, placebo-controlled studies of identical design were conducted to evaluate **BOTOX® COSMETIC** for use in the temporary improvement of the appearance of moderate to severe glabella facial lines. The studies enrolled healthy adults (ages 18 to 75) with glabella lines of at least moderate severity at maximum frown. Patients were excluded if they had ptosis, deep dermal scarring, or an inability to substantially lessen glabella lines even by physically spreading them apart. Subjects received a single treatment with **BOTOX® COSMETIC** (N=405, combined studies) or placebo (N=132, combined studies). 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 glabella line severity at maximum frown and the subject's global assessment of change in appearance of glabella 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 patients (6%) ≥ 65 years of age. Most of the subjects (82%) were women, and Caucasian (84%). At baseline, 210 patients (39%) had glabella line severity scores at rest of moderate or severe.

In these studies, the severity of glabella lines was reduced for up to 120 days in the **BOTOX® COSMETIC** group compared to the placebo group as measured both by investigator rating of glabella line severity at maximum frown (Table 1), and by subject's global assessment of change in appearance of glabella lines (Table 2).

TABLE 1.

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

DAY	BOTOX® COSMETIC	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	68% (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 parentheses

^b Day 30: Co-Primary Efficacy Time point, P<0.001

TABLE 2.

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

DAY	BOTOX® COSMETIC	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 parentheses

^b Day 30: Co-Primary Efficacy Time point, P<0.001

In the subset of patients 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® COSMETIC** treated patients (74%, 119/161) than placebo treated patients (20%, 10/49).

Analysis of the limited number of patients 65 years or older suggested lower treatment-associated response compared to patients less than 65 years of age. (Table 3).

TABLE 3.

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

ASSESSMENT	AGE GROUP	BOTOX® COSMETIC 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 parentheses

Exploratory analyses by gender suggested that responder rates in the **BOTOX® COSMETIC** 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 patients (n=64 in the **BOTOX® COSMETIC** treated group) the responder rates were similar to those observed in the Caucasian patients.

INDICATIONS AND USAGE

BOTOX® COSMETIC is indicated for the temporary improvement in the appearance of moderate to severe glabella lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

CONTRAINDICATIONS

BOTOX® COSMETIC 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

BOTOX® and **BOTOX® COSMETIC** contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® COSMETIC**.

Do not exceed the recommended dosage and frequency of administration of **BOTOX® COSMETIC**. 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® COSMETIC** should be discontinued and appropriate medical therapy immediately instituted.

Pre-Existing Neuromuscular Disorders

Caution should be exercised when administering **BOTOX[®] COSMETIC** 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 disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX[®] COSMETIC**. 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 is also a case report where a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

Cardiovascular System

There have been rare reports following administration of **BOTOX[®]** of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

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

General:

The safe and effective use of **BOTOX[®] COSMETIC** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX[®] COSMETIC** must understand the relevant neuromuscular and/or orbital anatomy of the area involved, as well as any alterations to the anatomy due to prior surgical procedures and avoid injection into vulnerable anatomic areas. Caution should be used when **BOTOX[®] COSMETIC** 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).

Reduced blinking from **BOTOX[®] COSMETIC** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of **BOTOX[®]** for the treatment of blepharospasm, 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.

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.

Caution should be used when **BOTOX[®] COSMETIC** treatment is used in patients who have an inflammatory skin problem 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 as these patients were excluded from the Phase 3 safety and efficacy trials.

Needle-related pain and/or anxiety may result in vasovagal responses, (including e.g., syncope, hypotension) which may require appropriate medical therapy.

Injection intervals of **BOTOX[®] COSMETIC** should be no more frequent than every three months and should be performed using the lowest effective dose (See: Adverse Reactions, Immunogenicity).

Information for Patients:

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

Drug Interactions:

Co-administration of **BOTOX[®] COSMETIC** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) 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

Administration of **BOTOX[®] COSMETIC** is not recommended during pregnancy. There are no adequate and well-controlled studies of **BOTOX[®] COSMETIC** in pregnant women. When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of **BOTOX[®] COSMETIC** was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification.

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[®] COSMETIC**.

If the patient becomes pregnant after the administration of this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations that 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[®] COSMETIC**.

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 testicular atrophy or 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[®] COSMETIC** is administered to a nursing woman.

Pediatric use: Use of **BOTOX[®] COSMETIC** is not recommended in children.

Geriatric use:

The two clinical studies of **BOTOX[®] COSMETIC** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, the responder rates appeared to be higher for patients younger than age 65 than for patients 65 years or older. (See: CLINICAL STUDIES)

There were too few patients (N=3) over the age of 75 to allow any meaningful comparisons.

ADVERSE REACTIONS

General:

BOTOX[®] and **BOTOX[®] COSMETIC** contain the same active ingredient in the same formulation. Therefore adverse events observed with the use of **BOTOX[®]** also have the potential to be associated with the use of **BOTOX[®] COSMETIC**.

The most serious adverse events reported after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, pneumonia, and/or other significant debility. 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 pre-existing cardiovascular disease. (See: WARNINGS). 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. Additionally, 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.

In general, adverse events occur within the first week following injection of **BOTOX[®] COSMETIC** and while generally transient may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema and/or bleeding/bruising may be associated with the injection.

Glabellar Lines:

In clinical trials of **BOTOX[®] COSMETIC** the most frequently reported adverse events following injection of **BOTOX[®] COSMETIC** were headache*, respiratory infection*, flu syndrome*, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site*, paresthesia* and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months or longer.

(* incidence not different from Placebo)

The data described in Table 4 reflect exposure to **BOTOX[®] COSMETIC** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX[®] COSMETIC** in the improvement of the appearance of glabellar lines (See: CLINICAL STUDIES). Adverse events of any cause were reported for 44% of the **BOTOX[®] COSMETIC** treated subjects and 42% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX[®] COSMETIC** treated arm than in placebo (3% vs. 0).

In the open-label, repeat injection study, blepharoptosis was reported for 2% (8/373) of subjects in the first treatment cycle and 1% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates 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.

TABLE 4.

Adverse Events Reported at Higher Frequency (>1%) in the BOTOX® COSMETIC Group Compared to the Placebo Group

Adverse Events by Body System	Percent of Patients Reporting Adverse Events	
	BOTOX® Cosmetic (N=405) %	Placebo (N=130) %
Overall	44	42
Body as a Whole Pain in Face	2	1
Skin and Appendages Skin Tightness	1	0
Digestive System Nausea Dyspepsia Tooth Disorder	3 1 1	2 0 0
Special Senses Blepharoptosis	3	0
Musculoskeletal System Muscle Weakness	2	0
Cardiovascular Hypertension	1	0

Immunogenicity:

Treatment with BOTOX® COSMETIC may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments with BOTOX® COSMETIC by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving BOTOX® COSMETIC has not been well studied.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin 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 the lowest effective dose given at the longest feasible intervals between injections.

Postmarketing Experience

Transient ptosis, the most frequently reported complication, has been reported in the literature in approximately 5% of patients. There has been a single report of diplopia, which resolved completely in three weeks.

The following other adverse reactions have been identified since the drug has been marketed:

abdominal pain; blurred vision; brachial plexopathy; decreased hearing; diarrhea; ear noise; erythema multiforme; fever; focal facial paralysis; glaucoma; localized numbness; loss of appetite; malaise; myalgia; myasthenia gravis; pruritus; psoriasisiform eruption; retinal vein occlusion; sweating; syncope; vertigo with nystagmus, and vomiting.

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BOTOX® COSMETIC

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 botulinum toxin.

Reporting Adverse Events

Adverse events following use of BOTOX® COSMETIC should be reported to the Pharmacovigilance Department, Allergan Inc. (1-800-433-8871). Adverse events may also be reported to the U. S. Department of Health and Human Services (DHHS) Adverse Event Reporting System. Report forms and reporting requirement information can be obtained from Adverse Event Reporting System (AERS) through a toll free number 1-800-822-7967.

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

For Intramuscular Injection Only

BOTOX® COSMETIC is to be reconstituted only with 0.9% sterile, non-preserved saline (100 Units in 2.5 mL saline) prior to intramuscular injection. The resulting formulation will be 4.0 Units per 0.1 mL and a total treatment dose of 20 Units in 0.5 mL. The duration of activity of BOTOX® COSMETIC for glabellar lines is approximately 3-4 months. The safety and effectiveness of more frequent dosing with BOTOX® COSMETIC has not been clinically evaluated and is not recommended.

Reconstituted BOTOX® COSMETIC should be clear, colorless and free of particulate matter.

BOTOX® COSMETIC is supplied as a single patient use vial. The product and diluent do not contain a preservative. Once opened and reconstituted it should be stored in a refrigerator (2° to 8°C) and used within four hours. Discard any remaining solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not freeze reconstituted BOTOX® COSMETIC.

Dilution Technique:

Using a 21-gauge needle and an appropriately sized syringe draw up a total of 2.5 mL of 0.9% sterile saline without a preservative. Insert the needle at a 45° angle and slowly inject into the BOTOX® COSMETIC vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently rotate the vial and record the date and time of reconstitution on the space on the label.

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-gauge needle. Confirm the patency of the needle.

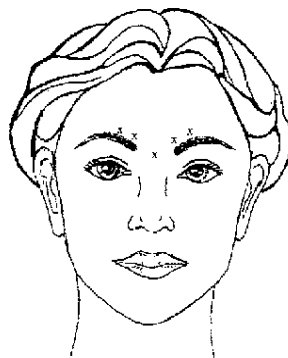
Injection Technique:

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 centimeter 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.

Using a 30-gauge needle, inject a dose of 0.1 mL into each of 5 sites, 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® COSMETIC induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.



HOW SUPPLIED:

BOTOX® COSMETIC is supplied in a single patient use vial. Each vial contains 100 Units of vacuum-dried *Clostridium botulinum* type A neurotoxin complex. NDC 0023-9232-01.

Vials of BOTOX® COSMETIC 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 fluorescent 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® COSMETIC should be stored in a refrigerator (2° to 8°C) for up to 24 months. Administer BOTOX® COSMETIC within 4 hours of reconstitution; during this period reconstituted BOTOX® COSMETIC should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX® COSMETIC should be clear, colorless and free of particulate matter. **Do not use after the expiration date on the vial.**

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

Reference:

1. Wang YC, Burr DH, Korthals GJ, Sugiyama H. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. *Appl Environ Microbiol* 1984; 48:951-955.