

BOTOX[®] Cosmetic
(onabotulinumtoxinA)
for injection

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

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of **BOTOX[®] Cosmetic** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.

DESCRIPTION

BOTOX[®] Cosmetic (onabotulinumtoxinA) for injection, 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, intended for intramuscular use. 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.

The primary release procedure for **BOTOX[®] Cosmetic** uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products **BOTOX[®]** and **BOTOX[®] Cosmetic**. One Unit of **BOTOX[®] Cosmetic** corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols, Units of biological activity of **BOTOX[®] Cosmetic** cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of **BOTOX[®] Cosmetic** is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX[®] Cosmetic** contains either 100 Units of *Clostridium botulinum* type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride or 50 Units of *Clostridium botulinum* type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg 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

Using currently available analytical technology, it is not possible to detect **BOTOX[®] Cosmetic** in the peripheral blood following intramuscular injection at the recommended doses.

CLINICAL STUDIES

Glabellar 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 glabellar facial lines. The studies enrolled healthy adults (ages 18 to 75) with glabellar 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 glabellar 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 glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines, both at Day 30 post-injection. For the investigator rating, using a 4-point grading scale (0=none, 3=severe) a responder was defined as having a severity grade of 0 or 1. For the subject's global assessment of change, the ratings were from +4 (complete improvement) to -4 (very marked worsening). A responder was defined as having a grade of at least +2 (moderate improvement). After completion of the randomized studies, subjects were offered participation in an open label, repeat treatment study to assess the safety of repeated treatment sessions.

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

In these studies, the severity of glabellar 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 glabellar line severity at maximum frown (Table 1), and by subject's global assessment of change in appearance of glabellar lines (Table 2).

TABLE 1.
Investigator's Assessment of Glabellar 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	69% (64, 74)
90	48% 192/403	2% 3/128	45% (40, 51)
120	25%	2%	24%

	102/403	2/128	(19, 29)
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^a 95% confidence intervals are shown in parenthesis

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

TABLE 2.

Subject's Assessment of Change in Appearance of Glabellar 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 parenthesis

^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 a 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 parenthesis

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 glabellar 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 botulinum toxin preparation or to any of the components 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**.

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

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX[®] Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX[®] Cosmetic cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method (see DESCRIPTION).

Spread of Toxin Effect

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

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

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

Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received **BOTOX[®]** injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. (Safety and effectiveness have not been established for indications pertaining to these

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

Hypersensitivity Reactions

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

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX**[®] **Cosmetic** (see **ADVERSE REACTIONS**).

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

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

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

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

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin (see **WARNINGS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY**).

Cardiovascular System

There have been 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

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 (see **WARNINGS**).

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

The physician should provide a copy of the FDA-Approved Patient Medication Guide and review the contents with the patient. Patients should be advised to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens.

Patients should be counseled that if loss of strength, muscle weakness, or impaired vision occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Drug Interactions

Co-administration of **BOTOX[®] Cosmetic** and aminoglycosides¹ 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 Units/kg. Higher doses (8 Units/kg or 16 Units/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 Units/kg/day (days 6 to 18 of gestation) and 2 Units/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 Units/kg was 4 Units/kg in male rats and 8 Units/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 spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, pneumonia, and/or other significant debility.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease (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. 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.

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	3	2

Dyspepsia	1	0
Tooth Disorder	1	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; psoriasiform eruption; retinal vein occlusion; sweating; syncope; vertigo with nystagmus; and vomiting.

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

Excessive doses of **BOTOX[®] Cosmetic** may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection (see **BOXED WARNING** and **WARNINGS**). These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened,

intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm>.

DOSAGE AND ADMINISTRATION

For Intramuscular Injection Only

BOTOX[®] Cosmetic is to be reconstituted only with 0.9% sterile, non-preserved saline prior to intramuscular injection. Per the dilution table below, draw up the required amount of 0.9% sterile non-preserved sodium chloride solution into a syringe to obtain a reconstituted solution at a concentration of 4 Units/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.

Dilution Table

Diluent Added to 100 Unit Vial (0.9% Sodium Chloride Injection Only)	Resulting Dose Units per 0.1 mL	Diluent Added to 50 Unit Vial (0.9% Sodium Chloride Injection Only)	Resulting Dose Units per 0.1 mL
2.5 mL	4 Units	1.25 mL	4 Units

Reconstituted **BOTOX[®] Cosmetic** should be clear, colorless, and free of particulate matter.

BOTOX[®] Cosmetic is supplied as a single 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 24 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/100 Unit vial or 1.25 mL/50 Unit vial 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 30-33 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 cm above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Do not inject toxin closer than 1 cm above the central eyebrow.

Using a 30-33 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 use vial in the following sizes:

50 Units: NDC 0023-3919-50

100 Units: 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 1-800-890-4345 from 7:00 AM to 3:00 PM 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 36 months for the 50 Units and 100 Units vials.

Administer **BOTOX[®] Cosmetic** within 24 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.



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MEDICATION GUIDE
BOTOX[®]
BOTOX[®] Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for Injection

Read the Medication Guide that comes with **BOTOX** or **BOTOX Cosmetic** before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening, including:

- **Problems breathing or swallowing**
- **Spread of toxin effects**

These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

1. Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of **BOTOX** or **BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.

- People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.

2. Spread of toxin effects. In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site

and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating,

blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary).

It is not known whether **BOTOX** is safe or effective in people younger than:

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

Who should not take BOTOX or BOTOX Cosmetic?

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc*[®], *Dysport*[®], or *Xeomin*[®]
- have a skin infection at the planned injection site
- are being treated for urinary incontinence and have a urinary tract infection (UTI)
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing)

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?

Tell your doctor about all your medical conditions, including if you:

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- have allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems
- have plans to have surgery
- had surgery on your face
- have weakness of your forehead muscles, such as trouble raising your eyebrows
- have drooping eyelids
- have any other change in the way your face normally looks
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*[®] (rimabotulinumtoxinB), *Dysport*[®] (abobotulinumtoxinA), or *Xeomin*[®] (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.

- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

What should I avoid while taking BOTOX or BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic may cause loss of strength or general muscle weakness, or vision problems within hours to weeks of taking BOTOX or BOTOX Cosmetic. If this happens, do not drive a car, operate machinery, or do other dangerous activities. See "What is the most important information I should know about BOTOX and BOTOX Cosmetic?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about BOTOX and BOTOX Cosmetic?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- urinary tract infection in people being treated for urinary incontinence
- inability to empty your bladder on your own and are being treated for urinary incontinence.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX or BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX and BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about BOTOX and BOTOX Cosmetic:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX and BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX and BOTOX Cosmetic** that is written for healthcare professionals. For more information about **BOTOX and BOTOX Cosmetic** call Allergan at 1-800-433-8871 or go to www.BOTOX.com.

What are the ingredients in BOTOX and BOTOX Cosmetic?

Active ingredient: botulinum toxin type A

Inactive ingredients: human albumin and sodium chloride

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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U.S. Patents 5,437,291; 5,714,468; 6,667,041; 6,683,049; 6,896,886; 6,974,578; 7,001,602; 7,429,387; and 7,449,192

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