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

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

Description: BOTOX® 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 (U) of **BOTOX® COSMETIC** 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® COSMETIC**. 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® COSMETIC** 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® 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:

Glabellar Lines:

Two phase 3 randomized, multi-center, double blind, placebo-controlled, parallel-group 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 adult patients (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Patients were excluded if they had an infection or skin problem at the injection site, history of facial nerve palsy, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, inability to substantially lessen glabellar lines even by physically spreading them apart or had a known history of neuromuscular disorder or other disorder that could interfere with neuromuscular function. Subjects received a single treatment of intramuscular injection with either **BOTOX® COSMETIC** (N=405, combined studies) or placebo (N=132, combined studies). Injection volume was 0.1ml/injection site, for a dose/injection site in the active treatment groups of 4U. Patients were to be 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 U.

The co-primary efficacy measurements were the investigator's rating of glabellar line severity at maximum frown at Day 30 post-injection and the subject's global assessment of change in appearance of glabellar lines at Day 30 post-injection. For the investigator rating, a photoguide was provided to each study center to assist in grading the severity of glabellar lines using a 4-point grading scale (0=none 1=mild 2= moderate 3=severe). A responder was defined as having a severity grade of 0 or 1.

For the global assessment of change in appearance of glabellar lines, the subject responded to the question, "How would you rate the change in the appearance of your glabellar lines compared with immediately before your most recent injection?" The ratings of responses by subjects were from +4 (complete improvement, about 100%) to -4 (very marked worsening, about 100% worse or greater). A responder was defined as having a grade of at least +2 (moderate improvement, about 50%).

A secondary efficacy endpoint was the investigator's rating of glabellar line severity at rest at Day 30 post-injection in those subjects who at baseline demonstrated a glabellar line severity score *at rest* of moderate or severe.

For the investigators' rating, the criteria for effectiveness was a 30 percentage point difference between **BOTOX® COSMETIC** and placebo treatment groups in the incidence of subjects with an investigator's rating of glabellar line severity of none or mild at maximum frown. For the subjects' rating, the criteria for effectiveness was a 25 percentage point difference between **BOTOX® COSMETIC** and placebo treatment groups in the incidence of subjects with a score of at least +2 (moderate improvement) in subject's global assessment of change in the appearance of glabellar lines.

The combined results of these two efficacy trials with the same design are presented here. There were 210 subjects (161 subjects in the **BOTOX® COSMETIC** treated group and 49 subjects in the placebo treated group) who had glabellar line severity scores at rest of moderate or severe.

The mean age was 46.0 years, with a range of 22 to 78 years. Of these, 68.2% (366/537) were ≤ 50 years of age and 31.8% (171/537) were ≥ 51 years of age and 6.0% were ≥ 65 years of age.

Most of the subjects were female, 81.9% (440/537) and Caucasian, 83.8% (450/537).

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 and at rest, and by subject's global assessment of change in appearance of glabellar lines. By Day 7, 74% (299/405) of subjects had achieved a severity score of none or mild at maximum frown by the investigator's assessment. This increased to 80% (325/405) by the primary efficacy endpoint day of Day 30, compared to 3% of placebo-treated patients (Table 1). By Day 7, 83% (334/405) of subjects assessed moderate or better improvement in their own appearance (+2 or better). This increased to 89% (362/405) by the primary efficacy endpoint day of Day 30, compared to 7% of placebo-treated patients (Table 2). Based on resting appearance as judged by the investigator, 68% (110/161) of subjects achieved a severity score of none or mild at Day 7, and 74% (119/161) by the efficacy endpoint day of Day 30 (Table 3).

Table 1.
Investigator's Assessment—Responder Rates Assessed at Maximum Frown (% and Number of Subjects with Severity of None or Mild)

DAY	BOTOX® COSMETIC	PLACEBO	DIFFERENCE[a]	P-VALUE
7	73.8% 299/405	6.1% 8/132	67.8% (61.9, 73.7)	<0.001
30*	80.2% 325/405	3.0% 4/132	77.2% (72.4, 82.1)	<0.001
60	70.2% 283/403	1.5% 2/130	68.7% (63.7, 73.6)	<0.001
90	47.6% 192/403	2.3% 3/128	45.3% (39.8, 50.8)	<0.001
120	25.3% 102/403	1.6% 2/128	23.8% (19.0, 28.5)	<0.001

[a] 95% confidence intervals are shown in parentheses
* Day 30: Co-Primary Efficacy Timepoint

Table 2.
Subject's Assessment—Responder Rates of Appearance (% and Number of Subjects with at Least Moderate Improvement)

DAY	BOTOX® COSMETIC	PLACEBO	DIFFERENCE[a]	P-VALUE
7	82.5% 334/405	9.1% 12/132	73.4% (67.2, 79.5)	<0.001
30*	89.4% 362/405	6.8% 9/132	82.6% (77.3, 87.8)	<0.001
60	81.9% 330/403	3.8% 5/130	78.0% (73.0, 83.1)	<0.001
90	63.0% 254/403	3.1% 4/128	59.9% (54.3, 65.5)	<0.001
120	39.0% 157/403	0.8% 1/128	38.2% (33.2, 43.2)	<0.001

[a] 95% confidence intervals are shown in parentheses
* Day 30: Co-Primary Efficacy Timepoint

Table 3.
Investigator's Assessment—Responder Rates Assessed at Rest in Subjects with Moderate or Severe Severity Score at Baseline (% and Number of Subjects with Severity of None or Mild)

DAY	BOTOX® COSMETIC	PLACEBO	DIFFERENCE[a]	P-VALUE
7	68.3% 110/161	24.5% 12/49	43.8% (29.8, 57.9)	<0.001
30*	73.9% 119/161	20.4% 10/49	53.5% (40.3, 66.7)	<0.001
60	72.7% 117/161	24.5% 12/49	48.2% (34.3, 62.1)	<0.001
90	70.8% 114/161	34.7% 17/49	36.1% (21.1, 51.2)	<0.001
120	59.0% 95/161	34.7% 17/49	24.3% (9.0, 39.7)	0.007

[a] 95% confidence intervals are shown in parentheses
* Day 30: Secondary Endpoint

The responder rates for both co-primary efficacy variables were higher for subjects ≤ 50 years of age than for those ≥ 51 years to ≤ 65 years of age (Tables 4 and 5). Efficacy was higher for both groups compared to those subjects ≥ 65 years of age (Tables 6 and 7). In the cervical dystonia trial, there was also a consistently observed treatment-associated effect between subsets greater than and less than 65 years of age. (See Precautions: Geriatrics) There were no statistically significant between-group differences for the investigator's assessment at maximum frown for this age group. There was a statistically significant difference in favor of **BOTOX® COSMETIC** for the subject's global assessment at all time points except Day 120 ($p \leq 0.036$).

Table 4.
Investigator's Assessment—Responder Rates of Glabellar Line Severity by Age Distribution

	Investigator's Assessment at Maximum Frown % rated 0 or 1 ≤ 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 50 years		Investigator's Assessment at Maximum Frown % rated 0 or 1 > 65 years	
DAY	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo
7	80.7% 226/280	5.8% 5/86	58.4% 73/125	6.5% 3/46	34.8% 8/23	11.1% 1/9
30*	84.6% 237/280	2.3% 2/86	70.4% 88/125	4.3% 2/46	39.1% 9/23	22.2% 2/9
60	73.6% 206/280	1.2% 1/85	62.6% 77/123	2.2% 1/45	30.4% 7/23	12.5% 1/8
90	50.4% 141/280	1.2% 1/83	41.5% 51/123	4.4% 2/45	30.4% 7/23	12.5% 1/8
120	28.6% 80/280	0% 0/83	17.9% 22/123	4.4% 2/45	4.3% 1/23	12.5% 1/8

* Day 30: Co-Primary Efficacy Timepoint

Table 5.
Subject's Assessment—Responder Rates of Glabellar Line Severity by Age Distribution

	Subject's Assessment % +2 or better ≤ 50 years		Subject's Assessment % +2 or better > 50 years		Subject's Assessment % +2 or better > 65 years	
DAY	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo
7	86.8% 243/280	7.0% 6/86	72.8% 91/125	13.0% 6/46	52.2% 12/23	11.1% 1/9
30*	91.8% 257/280	3.5% 3/86	84.0% 105/125	13.0% 6/46	69.6% 16/23	11.1% 1/9
60	84.6% 237/280	3.5% 3/85	75.6% 93/123	4.4% 2/45	65.2% 15/23	0% 0/8
90	63.2% 177/280	2.4% 2/83	62.6% 77/123	4.4% 2/45	65.2% 15/23	0% 0/8
120	41.1% 115/280	1.2% 1/83	34.1% 42/123	0% 0/45	17.4% 4/23	0% 0/8

* Day 30: Co-Primary Efficacy Timepoint

Table 6.
Investigators Assessment—Responder Rates at Maximum Frown (% and Number of Subjects with Severity of None or Mild) for Subjects >65 Years of Age

DAY	BOTOX® COSMETIC N=23	PLACEBO N=9	DIFFERENCE	RELATIVE RISK	P-VALUE
7	34.8% 8/23	11.1% 1/9	23.67 (-4.62, 51.96)	3.13 (0.45, 21.58)	0.188
30*	39.1% 9/23	22.2% 2/9	16.91 (-16.8, 50.61)	1.76 (0.47, 6.62)	0.373
60	30.4% 7/23	12.5% 1/8	17.93 (-11.7, 47.58)	2.43 (0.35, 16.85)	0.326
90	30.4% 7/23	12.5% 1/8	17.93 (-11.7, 47.58)	2.43 (0.35, 16.85)	0.326
120	4.3% 1/23	12.5% 1/8	-8.15% (-32.5, 16.23)	0.35 (0.02, 4.94)	0.426

* Day 30: Co-Primary Efficacy Timepoint

TABLE 7.
Subject's Assessment—Responder Rates at Maximum Frown (% and Number of Subjects with Severity of None or Mild) for Subjects >65 Years of Age

DAY	BOTOX® COSMETIC N=23	PLACEBO N=9	DIFFERENCE	RELATIVE RISK	P-VALUE
7	52.2% 12/23	11.1% 1/9	41.06 (12.11, 70.02)	4.70 (0.71, 31.05)	0.036
30*	69.6% 16/23	11.1% 1/9	58.45 (30.61, 86.30)	6.26 (0.97, 40.52)	0.003
60	65.2% 15/23	0% 0/8	65.22 (45.75, 84.68)	11.63 (0.77, 174.7)	0.002
90	65.2% 15/23	0% 0/8	65.22 (45.75, 84.68)	11.63 (0.77, 174.7)	0.002
120	17.4% 4/23	0% 0/8	17.39 (1.90, 32.88)	3.38 (0.20, 56.59)	0.214

* Day 30: Co-Primary Efficacy Timepoint

Exploratory analyses of subsets by patient gender suggest that both genders receive benefit, although female patients may receive somewhat greater amounts than male patients. The responder rates for both co-primary efficacy variables were higher for female subjects than for males (Tables 8 and 9).

TABLE 8.
Investigator's Assessment—Responder Rates of Glabellar Line Severity by Gender

	Investigator's Assessment At Maximum Frown % rated 0 or 1 FEMALE	Investigator's Assessment At Maximum Frown % rated 0 or 1 MALE
DAY	BOTOX® COSMETIC	BOTOX® COSMETIC
30*	84.7% 283/334	59.2% 42/71
120	27.7% 92/332	14.1% 10/71

* Day 30: Co-Primary Efficacy Timepoint

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TABLE 9.
Subject's Assessment—Responder Rates of Glabellar Line Severity by Gender

	Subject's Assessment % +2 or better FEMALE	Subject's Assessment % +2 or better MALE
DAY	BOTOX® COSMETIC	BOTOX® COSMETIC
30*	93.1% 311/334	71.8% 51/71
120	42.8% 142/332	21.1% 15/71

* Day 30: Co-Primary Efficacy Timepoint

There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets. The responder rates for both co-primary efficacy variables were slightly higher for Caucasian than for non-Caucasian subjects (Tables 10 and 11).

TABLE 10.
Investigator's Assessment—Responder Rates of Glabellar Line Severity by Race

	Investigator's Assessment At Maximum Frown % rated 0 or 1 CAUCASIAN	Investigator's Assessment At Maximum Frown % rated 0 or 1 NON-CAUCASIAN
DAY	BOTOX® COSMETIC	BOTOX® COSMETIC
30*	81.2% 277/341	75.0% 48/64
120	25.7% 87/339	23.4% 15/64

* Day 30: Co-Primary Efficacy Timepoint

TABLE 11.
Subject's Assessment—Responder Rates of Glabellar Line Severity by Race

	Subject's Assessment % +2 or better CAUCASIAN	Subject's Assessment % +2 or better NON-CAUCASIAN
DAY	BOTOX® COSMETIC	BOTOX® COSMETIC
30*	89.7% 306/341	87.5% 56/64
120	40.1% 136/339	32.8% 21/64

* Day 30: Co-Primary Efficacy Timepoint

Responder rates for both co-primary efficacy variables tended to be lower for subjects with a severe baseline score at maximum frown compared to subjects with a moderate baseline score (Tables 12 and 13). The proportion who had their score rated as none to mild at rest after treatment was higher in the **BOTOX® COSMETIC** treated group as compared to the placebo treated group ($p \leq 0.022$) for every time-point beginning at Day 7 through Day 120 in study 010 and through Day 90 in study 023.

TABLE 12.
Investigator's Assessment—Responder Rates of Glabellar Line Severity by Baseline Glabellar Line Severity at Maximum Frown

	Investigator's Assessment At Maximum Frown % rated 0 or 1 MODERATE		Investigator's Assessment At Maximum Frown % rated 0 or 1 SEVERE	
DAY	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo
30*	95.8% 159/166	1.8% 1/56	69.5% 166/239	1.4% 1/74
120	39.6% 65/164	1.8% 1/55	15.5% 37/238	1.4% 1/73

* Day 30: Co-Primary Efficacy Timepoint

TABLE 13.
Subject's Assessment–Responder Rates of Glabellar Line Severity by Baseline Glabellar Line Severity

	Subject's Assessment % +2 or better MODERATE		Subject's Assessment % +2 or better SEVERE	
DAY	BOTOX® COSMETIC	Placebo	BOTOX® COSMETIC	Placebo
30*	94.0% 156/166	7.1% 4/56	86.2% 206/239	4.1% 3/74
120	50.6% 83/164	0% 0/55	31.0% 74/239	1.4% 1/73

* Day 30: Co-Primary Efficacy Timepoint.

On completion of the efficacy trial, participants were invited to participate in a multicenter, open-label, non-comparative study to evaluate the safety of repeated treatments with **BOTOX® COSMETIC** using the same dose and procedure from the previous studies. Only patients who had a glabellar line severity rating of mild or greater at maximum frown at the time of enrollment were admitted to the open-label safety evaluation study. A total of 373 subjects (72.6%) were enrolled in this open-label study and 318 subjects completed the study. There were a total of 258 subjects who received **BOTOX® COSMETIC** in the previous trials and both injections of **BOTOX® COSMETIC** during this trial (for a total treatment time of 12 months). Of these, 239 subjects completed the 120 days of follow-up after the final injection. The open-label study was designed specifically to evaluate the safety of repeated treatments. In the open-label, repeat injection study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (183/373) of subjects.

Cosmetic 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 $\leq$ 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:
Do not exceed the recommended dosage and frequency of administration of **BOTOX® COSMETIC.** Risks resulting from administration at higher dosages are not known.

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 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.

There have also been rare reports following administration of BOTOX for other indications 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.

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: Epinephrine should be available or other precautionary methods taken as necessary should an anaphylactic reaction occur.

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 and any alterations to the anatomy due to prior surgical procedures. 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.

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[1] 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: Clinical studies of **BOTOX® COSMETIC** did not include sufficient numbers of subjects aged 65 and over to determine statistically whether they respond differently from younger subjects. However, in the two identical phase 3 randomized 3:1, multi-center, double blind, placebo-controlled, parallel-group efficacy studies, the responder rates for both co-primary efficacy variables were higher for subjects ≤ 50 years of age compared to those subjects ≥ 65 years of age. Analysis based on a combined data set showed that, for the investigator's assessment endpoint of subjects aged 65 and over at Day 30, 39% (9/23) of subjects were responders compared to 22% (2/9) in the placebo group. This difference is neither statistically different (p= 0.228) nor exceeds the pre-specified 30-percentage-point difference required by the definition of clinically significant. There were no statistically significant between-group differences for the investigator's assessment at maximum frown for this age group. There was a statistically significant difference in favor of **BOTOX® COSMETIC** for the subject's global assessment at at all time points (p ≤0.036) except Day 120 (p = 0.214). (See Clinical Trials Section)

There were too few patients over the age of 75 to allow any meaningful 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 cardiac function and of concomitant disease or other drug therapy.

Adverse Reactions:
General:
The most serious adverse events reported for other indications studied include rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, 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 pre-existing cardiovascular disease (See Warnings). 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.

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 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.

The data described in Table 14 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 43.7% of the **BOTOX® COSMETIC** treated subjects and 41.5% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX® COSMETIC** treated arm than in placebo (3.2% vs. 0%, p-value = 0.045).

In the open-label, repeat injection study, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49.1% (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 14.
Randomized Double Blind Studies: Rates of Adverse Events Reported by >2 or more Subjects in the BOTOX® Cosmetic Group, by Treatment Group.

Adverse Event (in order of decreasing frequency for BOTOX® Cosmetic	BOTOX® Cosmetic (N=405)	Placebo (N=130)
Overall	177 (43.7%)	54 (41.5%)
Body as a Whole		
Headache	54 (13.3%)	23 (17.7%)
Pain in Face	9 (2.2%)	1 (0.8%)
Flu Syndrome	8 (2.0%)	2 (1.5%)
Pain at Injection Site	7 (1.7%)	1 (0.8%)
Edema at Injection Site	6 (1.5%)	3 (2.3%)
Pain in back	4 (1.0%)	3 (2.3%)
Injury accidental	3 (0.7%)	1 (0.8%)
Respiratory System		
Infection	14 (3.5%)	5 (3.8%)
Bronchitis	6 (1.5%)	1 (0.8%)
Sinusitis	6 (1.5%)	1 (0.8%)
Pharyngitis	5 (1.2%)	2 (1.5%)
Dyspnea	3 (0.7%)	0 (0.0%)
Infection sinus	3 (0.7%)	2 (1.5%)
Laryngitis	3 (0.7%)	0 (0.0%)
Rhinitis	3 (0.7%)	2 (1.5%)
Skin and Appendages		
Erythema	7 (1.7%)	2 (1.5%)
Skin Tightness	4 (1.0%)	0 (0.0%)
Irritation Skin	3 (0.7%)	0 (0.0%)
Digestive System		
Nausea	12 (3.0%)	3 (2.3%)
Dyspepsia	4 (1.0%)	0 (0.0%)
Tooth Disorder	4 (1.0%)	0 (0.0%)
Liver Function Abnormal	3 (0.7%)	2 (1.5%)
Special Senses		
Blepharoptosis	13 (3.2%)	0 (0.0%)
Nervous System		
Dizziness	5 (1.2%)	2 (1.5%)
Paresthesia	4 (1.0%)	1 (0.8%)
Anxiety	3 (0.7%)	0 (0.0%)
Twitch	3 (0.7%)	0 (0.0%)
Musculoskeletal System		
Muscle Weakness	8 (2.0%)	0 (0.0%)
Urogenital System		
Infection Urinary Tract	4 (1.0%)	1 (0.8%)
Hemic and Lymphatic System		
Ecchymosis	7 (1.7%)	3 (2.3%)
Cardiovascular		
Hypertension	4 (1.0%)	0 (0.0%)

In published literature of the use of botulinum toxin type A for facial lines, there has been a single reported incident of diplopia, which resolved completely in three weeks. Transient ptosis, the most frequently reported complication, has been reported in the literature in approximately 5% of patients.

Immunogenicity:
Treatment with **BOTOX® COSMETIC** for cosmetic purposes may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments with **BOTOX® COSMETIC** for glabellar lines or **BOTOX®** for other indications. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX® COSMETIC** treatment of the appearance of glabellar lines and the effectiveness of **BOTOX®** in the treatment of other clinical indications such as cervical dystonia, blepharospasm and strabismus 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 of the use of **BOTOX®** in the treatment of other clinical indications 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 the lowest effective dose given at the longest feasible intervals between injections.

Passive Adverse Event Surveillance

The following adverse reactions have been identified since the drug has been marketed: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction. 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.

Between January 1, 1990 and August 31, 2000, there have been 7 spontaneous reports of serious adverse events documented as being related to the reported cosmetic use of **BOTOX®**, including anaphylactic reaction, myasthenia gravis, decreased hearing, ear noise and localized numbness, blurred vision and retinal vein occlusion, glaucoma, and vertigo with nystagmus.

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 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 U per 0.1 mL and a total treatment dose of 20 U 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 in 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**.

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.

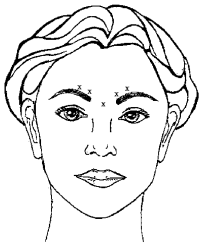
Dilution Technique:
Using a 21-gauge needle and an appropriately sized syringe draw up a total of 2.5 mL of 0.9% sterile saline. Insert the needle at a 45° angle and slowly inject into the **BOTOX® COSMETIC** vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently rotate the 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 "arrowhead" 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.
- Medial 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 U. 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 U of vacuum-dried *Clostridium botulinum* type A neurotoxin complex. NDC 0023-9232-01.

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. Do not use after the expiration date on the vial. 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. 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

References:

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.