HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOTOX® COSMETIC safely and effectively. See full prescribing information for BOTOX COSMETIC.

BOTOX COSMETIC (onabotulinumtoxinA) for injection, for intramuscular use
Initial U.S. Approval: 1989

WARNING: DISTANT SPREAD OF TOXIN EFFECT
See full prescribing information for complete boxed warning.
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 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, particularly in those patients who have an underlying condition that would predispose them to these symptoms. *(5.2)*

INDICATIONS AND USAGE

BOTOX Cosmetic is an acetylcholine release inhibitor and a neuromuscular blocking agent 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 (1)

DOSAGE AND ADMINISTRATION

- Administration: 0.1 mL (4 Units) by intramuscular injection into each of 5 sites, for a total dose of 20 Units (2.1)
- Dosage and administration recommendations should be followed; In treating adults for more than one approved indications with **BOTOX** and **BOTOX Cosmetic**, do not exceed a total dose of 360 Units administered in a 3 month interval (2.1)
- See Preparation and Dilution Technique for instructions on **BOTOX Cosmetic** reconstitution, storage, and preparation before injection (2.2)

DOSAGE FORMS AND STRENGTHS

For Injection: 50 Units or 100 Units vacuum-dried powder in a single-use vial for reconstitution (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4 1, 5.4)
- Infection at the injection site (4.2)

WARNINGS AND PRECAUTIONS

- Potency Units of **BOTOX Cosmetic** are not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.7)
- Care should be taken when injecting in or near vulnerable anatomic structures (5.3)
- Adverse event reports have been received involving the cardiovascular system, some with fatal outcomes. Use caution when administering to patients with pre-existing cardiovascular disease. (5.5)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.6)
- Use with caution in patients with compromised respiratory function or dysphagia (5.7)

ADVERSE REACTIONS

The most common adverse reaction (approximately 3%) was eyelid ptosis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Patients receiving concomitant treatment of **BOTOX Cosmetic** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of **BOTOX Cosmetic** may be potentiated (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: 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, 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 an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses. ***[See Warnings and Precautions (5.2)]***

1 INDICATIONS AND USAGE

BOTOX Cosmetic (onabotulinumtoxinA) for injection 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.

2 DOSAGE AND ADMINISTRATION

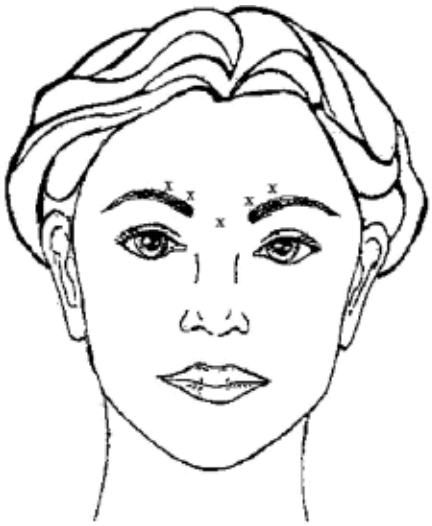
2.1 Instructions for Use

The potency Units of BOTOX Cosmetic (onabotulinumtoxinA) for injection 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 nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

Using a 30-33 gauge needle, inject a dose of 0.1 mL (4 Units) intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units (see Figure 1). 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.

The duration of effect 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.

Figure 1:



In treating adult patients for one or more indications with **BOTOX** and **BOTOX Cosmetic**, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

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 *[see Warnings and Precautions (5.3)]*.

2.2 Preparation and Dilution Technique

BOTOX Cosmetic is supplied in single-use 50 Units and 100 Units per vial. Prior to intramuscular injection, reconstitute each vacuum-dried vial of **BOTOX Cosmetic** with sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size needle and 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 (see Table 1). Then slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX Cosmetic** with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX Cosmetic** should be administered within 24 hours after reconstitution. During this time period, reconstituted **BOTOX Cosmetic** should be stored in a refrigerator (2° to 8°C). BOTOX Cosmetic vials are for single-use only. Discard any remaining solution.

Table 1: Dilution Instructions for BOTOX Cosmetic Vials (100 Units and 50 Units)

Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 50 Unit Vial	Resulting Dose Units per 0.1 mL
2.5 mL	4 Units	1.25 mL	4 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

Reconstituted **BOTOX Cosmetic** should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit. Do not freeze reconstituted **BOTOX Cosmetic**.

2.3 Administration

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.

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. Inject a dose of 0.1 mL (4 Units) intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units (see Figure 1).

3 DOSAGE FORMS AND STRENGTHS

- For injection: 50 Units, vacuum-dried powder in a single use vial for reconstitution
- For injection: 100 Units, vacuum-dried powder in a single use vial for reconstitution

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX Cosmetic is contraindicated in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions (5.4)]*.

4.2 Infection at the Injection Site(s)

BOTOX Cosmetic is contraindicated in the presence of infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 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 nor converted into units of any other botulinum toxin products assessed with any other specific assay method [*see Description (11)*].

5.2 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, 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 an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, 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. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory difficulties occur.

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), strabismus, or chronic migraine at the labeled doses have been reported.

5.3 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. Safety and effectiveness have not been established for indications pertaining to these injection sites. Some patients had pre-existing dysphagia or significant debility. 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.

5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, 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.

5.5 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. Use caution when administering to patients with pre-existing cardiovascular disease.

5.6 Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction 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 Warnings and Precautions (5.7)]*.

5.7 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 and Precautions (5.2)]*.

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 with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence

of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

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 and Precautions (5.2)]*.

5.8 Pre-existing Conditions at the Injection Site

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).

Caution should be used when **BOTOX Cosmetic** treatment is used in patients who have 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.

5.9 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

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. 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.

5.10 Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus

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.

5.11 Human Albumin and Transmission of Viral Diseases

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) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

6 ADVERSE REACTIONS

The following adverse reactions to **BOTOX Cosmetic** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Contraindications (4.1) and Warnings and Precautions (5.4)]*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the 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 reflect the rates observed in clinical practice.

BOTOX and **BOTOX Cosmetic** contain the same active ingredient in the same formulation, but have different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX** also have the potential to be observed with the use of **BOTOX Cosmetic**.

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

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.2)]*.

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 2 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 (14)]*. 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.

Table 2: Adverse Events Reported at Higher Frequency (>1%) in the BOTOX Cosmetic Group Compared to the Placebo Group

	Percent of Patients Reporting Adverse Events	
Adverse Events by Body System	**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

6.2 Immunogenicity

Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

The rate of formation of neutralizing antibodies in patients receiving **BOTOX Cosmetic** has not been well studied. 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 with the lowest effective dose given at the longest feasible intervals between injections. The critical factors for neutralizing antibody formation have not been well characterized.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to **BOTOX Cosmetic** with the incidence of antibodies to other products may be misleading.

6.3 Post-marketing Experience

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 drug exposure.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.4, 5.7)]*.

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 cardiovascular disease.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events.

The following adverse reactions by System Organ Class have been identified during post-approval use of **BOTOX/BOTOX Cosmetic**:

Ear and labyrinth disorders
Hypoacusis; tinnitus; vertigo

Eye disorders
Diplopia; strabismus; visual disturbances; vision blurred

Gastrointestinal disorders
Abdominal pain; diarrhea; dry mouth; nausea; vomiting

General disorders and administration site conditions
Denervation; malaise; pyrexia

Metabolism and nutrition disorders
Anorexia

Musculoskeletal and connective tissue disorders
Muscle atrophy; myalgia

Nervous system disorders
Brachial plexopathy; dysarthria; facial palsy; hypoaesthesia; localized numbness; myasthenia gravis; paresthesia; peripheral neuropathy; radiculopathy; syncope

Respiratory, thoracic and mediastinal disorders
Aspiration pneumonia; dyspnea; respiratory depression and/or respiratory failure

Skin and subcutaneous tissue disorders
Alopecia, including madarosis; hyperhidrosis; pruritus; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption)

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with **BOTOX Cosmetic** (onabotulinumtoxinA) for injection.

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

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

7.2 Anticholinergic Drugs

Use of anticholinergic drugs after administration of **BOTOX Cosmetic** may potentiate systemic anticholinergic effects.

7.3 Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin products 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.

7.4 Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX Cosmetic**.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.
There are no adequate and well-controlled studies in pregnant women. **BOTOX Cosmetic** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When **BOTOX Cosmetic** (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 12 times the average high human dose for glabellar lines of 20 Units on a body weight basis (Units/kg).

When **BOTOX Cosmetic** was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats is approximately 3 times the average human dose based on Units/kg, and the developmental no-effect dose of 0.25 Units/kg in rabbits are less than the average high human dose based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 48 times the average high human dose based on Units/kg.

8.3 Nursing Mothers

It is not known whether **BOTOX Cosmetic** 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.

8.4 Pediatric Use

Safety and effectiveness in patients below the age of 18 years have not been established.

8.5 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 (14)]*.

10 OVERDOSAGE

Excessive doses of **BOTOX Cosmetic** (onabotulinumtoxinA) for injection 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, these patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. 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 and Precautions (5.2, 5.7)]*.

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.

11 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 (LD_{50}) 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 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride; or 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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**.

12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with **BOTOX Cosmetic** (onabotulinumtoxinA) for injection.

12.3 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals have not been performed to evaluate carcinogenic potential of **BOTOX Cosmetic**.

Mutagenesis

BOTOX Cosmetic was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicologic assays.

Impairment of Fertility

In fertility studies of **BOTOX Cosmetic** (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately 12-24 times the average high human dose for glabellar lines of 20 Units on a body weight basis (Units/kg).

14 CLINICAL STUDIES

Two phase 3 randomized, multi-center, double-blind, placebo-controlled trials 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 trials enrolled healthy adults (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Subjects 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 trials) or placebo (N=132, combined trials). 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 subjects (6%) ≥ 65 years of age. Most of the subjects were women (82%), and Caucasian (84%). At baseline, 210 subjects (39%) had glabellar line severity scores at rest of moderate or severe.

In these trials, 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 3), and by subject's global assessment of change in appearance of glabellar lines (Table 4).

Table 3: 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% 102/403	2% 2/128	24% (19, 29)

[a] 95% confidence intervals are shown in parenthesis
[b] Day 30: Co-Primary Efficacy Time point, p<0.001

Table 4: 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 subjects 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 subjects (74%, 119/161) than placebo treated subjects (20%, 10/49).

Analysis of the limited number of subjects 65 years or older suggested a lower treatment-associated response compared to subjects less than 65 years of age (Table 5).

Table 5: 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 subjects (n=64 in the **BOTOX Cosmetic** treated group) the responder rates were similar to those observed in the Caucasian subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

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/lot 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.

Storage
Unopened vials of **BOTOX Cosmetic** should be stored in a refrigerator (2° to 8°C). Do not use after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Provide a copy of the Medication Guide and review the contents with the patient.

17.1 Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

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 *[see Boxed Warning and Warnings and Precautions (5.2, 5.7)]*.

17.2 Ability to Operate Machinery or Vehicles

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

Manufactured by: Allergan Pharmaceuticals Ireland
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