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 Halir 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.

One Unit of BOTOX Cosmetic corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. The method utilized for performing the assay is specific to Allergan’s product, BOTOX Cosmetic. To specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD50 assays, Units of biological activity of BOTOX Cosmetic cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed by laboratory protocols for the various mouse LD50 assays. Units of biological activity of BOTOX Cosmetic correspond to the calculated median intraperitoneal lethal dose (LD50) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX Cosmetic.

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 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.

The combined results of these two efficacy trials are presented here. The mean age was 46 years, with 32 patients (8%) > 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.

<table>
<thead>
<tr>
<th>Day</th>
<th>BOTOX Cosmetic</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>74%</td>
<td>6%</td>
<td>68% (0.001)</td>
</tr>
<tr>
<td>30</td>
<td>80%</td>
<td>3%</td>
<td>77% (0.001)</td>
</tr>
<tr>
<td>60</td>
<td>70%</td>
<td>2%</td>
<td>69% (0.001)</td>
</tr>
<tr>
<td>90</td>
<td>48%</td>
<td>2%</td>
<td>45% (0.001)</td>
</tr>
<tr>
<td>120</td>
<td>25%</td>
<td>2%</td>
<td>24% (0.001)</td>
</tr>
</tbody>
</table>

* 95% confidence intervals are shown in parenthesis

* 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).
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 approvedbotulinumtoxins 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 may 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 blepharon spasms at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported.

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 swallowing or breathing. 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 may 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 and avoid injection into vulnerable anatomic areas.

Caution should be used when BOTOX® Cosmetic treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Reduced blinking from BOTOX® Cosmetic injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of BOTOX® for the treatment of blepharon spasms, 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 amnoglycosides 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 only be performed with caution as the effect of the toxin may be potentiated.

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.
The reproductively 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 in approximately 5% of patients. There has been a single report of diplopia, which resolved completely in three weeks.

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.

Glabellar Lines
In clinical trials of BOTOX Cosmetic the most frequently reported adverse event following injection of BOTOX Cosmetic were headache, respiratory infection, flu syndrome, blepharoptosis and nausea.

CLINICAL STUDIES
Adverse Events by Body System

<table>
<thead>
<tr>
<th>Adverse Events by Body System</th>
<th>Percent of Patients Reporting Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX Cosmetic (N=405)</td>
</tr>
<tr>
<td>Overall</td>
<td>44</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
</tr>
<tr>
<td>Pain in Face</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td></td>
</tr>
<tr>
<td>Skin Tightness</td>
<td>1</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
</tr>
<tr>
<td>Tooth Disorder</td>
<td>1</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
</tr>
<tr>
<td>Blepharoptosis</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td></td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>2</td>
</tr>
<tr>
<td>Cardiovascular Hypertension</td>
<td>1</td>
</tr>
</tbody>
</table>

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

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting the lowest effective dose given at the longest feasible intervals between injections.

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

The following other adverse reactions have been identified since the drug has been marketed: abdominal pain; blurred vision; brachial plexopathy; decreased hearing; diarrhea; ear noise; erythema multiforme; fever; focal facial paralysis; glaucoma; localized numbness; loss of appetite; malaise; myalgia; myasthenia gravis; pruritus; psoriasisiform eruption; retinal vein occlusion; sweating; syncope; vertigo with nystagmus; and vomiting.

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. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis (see WARNINGS and PRECAUTIONS). Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or muscle paralysis.

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 1-770-468-7100. More information can be obtained at http://www.cdc.gov/ncidod/srp/drugs/drug-service.html.
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.

### Injection Technique

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 BOTOX Cosmetic for glabellar lines are 2-3 units.

- Do not inject toxin closer than 1 cm above the central eyebrow.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

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 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 30-33 gauge needle, and use 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:

1. Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
2. Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
3. Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
4. Do not inject toxin closer than 1 cm above the central eyebrow.

### Dilution Table

<table>
<thead>
<tr>
<th>Diluent Added to 100 Unit Vial (0.9% Sodium Chloride Injection Only)</th>
<th>Resulting Dose Units per 0.1 mL</th>
<th>Diluent Added to 50 Unit Vial (0.9% Sodium Chloride Injection Only)</th>
<th>Resulting Dose Units per 0.1 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mL</td>
<td>4 Units</td>
<td>1.25 mL</td>
<td>4 Units</td>
</tr>
</tbody>
</table>

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.

### Storage

Unopened vials of BOTOX Cosmetic should be stored in a refrigerator (2° to 8°C) for up to 36 months for the 100 Unit vial or up to 24 months for the 50 Unit vial.

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.

**Rx Only**

**Single use vial.**

**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.
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. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

- Problems swallowing, speaking, or breathing. These problems can happen hours 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 patients 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.
- 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 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?”

What are BOTOX and BOTOX Cosmetic?

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

- 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 patients younger than:

- 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 patients 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:

- have 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

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?”
- allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- a breathing problem, such as asthma or emphysema
• swallowing problems
• bleeding problems
• plans to have surgery
• had surgery on your face
• weakness of your forehead muscles, such as trouble raising your eyebrows
• drooping eyelids
• any other change in the way your face normally looks
• 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

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 or skin.
• 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.
• 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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