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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)*

RECENT MAJOR CHANGES

- Warnings and Precautions, Dry Eye in Patients Treated with BOTOX Cosmetic *(5.10)* 11/2019

INDICATIONS AND USAGE

BOTOX Cosmetic is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated in adult patients for the temporary improvement in the appearance of (*1*):

- Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity
- Moderate to severe lateral canthal lines associated with orbicularis oculi activity
- Moderate to severe forehead lines associated with frontalis muscle activity

DOSAGE AND ADMINISTRATION

- Botox Cosmetic is administered by intramuscular injection
- Glabellar Lines Administration: 0.1 mL (4 Units) into each of 5 sites, for a total dose of 20 Units (*2.3*)
- Lateral Canthal Lines Administration: 0.1 mL (4 Units) into each of 3 sites per side (6 total injection points), for a total of 24 Units (*2.3*)
- Forehead Lines Administration: 0.1 mL (4 Units) into each of 5 forehead line sites (20 Units) with 0.1 mL (4 Units) into each of 5 glabellar line sites (20 Units), for a recommended total of 40 Units (*2.3*)
- Follow dosage and administration recommendations. In treating adults for more than one approved indications with BOTOX and BOTOX Cosmetic, do not exceed a total dose of 400 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*)
- Potential serious adverse reactions after administration of BOTOX for unapproved uses (*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 reactions are (*6.1*):

- Glabellar Lines: eyelid ptosis (3%)
- Lateral Canthal Lines: eyelid edema (1%)
- Forehead Lines: headache (9%) and brow ptosis (2%)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 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: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION
WARNING: DISTANT SPREAD OF TOXIN EFFECT
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Instructions for Safe Use
2.2 Preparation and Dilution Technique
2.3 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
4.1 Known Hypersensitivity to Botulinum Toxin
4.2 Infection at the Injection Site(s)
5 WARNINGS AND PRECAUTIONS
5.1 Lack of Interchangeability between Botulinum Toxin Products
5.2 Spread of Toxin Effect
5.3 Serious Adverse Reactions with Unapproved Use
5.4 Hypersensitivity Reactions
5.5 Cardiovascular System
5.6 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders
5.7 Dysphagia and Breathing Difficulties
5.8 Pre-existing Conditions at the Injection Site
5.9 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm
5.10 Dry Eye in Patients Treated with BOTOX Cosmetic
5.11 Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus
5.12 Human Albumin and Transmission of Viral Diseases
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.3 Post-marketing Experience
7 DRUG INTERACTIONS
7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission
7.2 Anticholinergic Drugs
7.3 Other Botulinum Neurotoxin Products
7.4 Muscle Relaxants
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE

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For current labeling information, please visit https://www.fda.gov/drugsatfda

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Glabellar Lines
14.2 Lateral Canthal Lines
14.3 Forehead Lines
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*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 spasticity and at lower doses. ***[see Warnings and Precautions (5.2)]***

1 INDICATIONS AND USAGE

BOTOX Cosmetic (onabotulinumtoxinA) is indicated in adult patients for the temporary improvement in the appearance of:

- moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity
- moderate to severe lateral canthal lines associated with orbicularis oculi activity
- moderate to severe forehead lines associated with frontalis muscle activity

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe 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 Warnings and Precautions (5.1) and Description (11)]*.

Indication specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications with BOTOX and BOTOX Cosmetic, the maximum cumulative dose should generally not exceed 400 Units, in a 3 month interval.

The safety and effectiveness of dosing with BOTOX Cosmetic more frequently than every 3 months have not been clinically evaluated.

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 structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease.

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Do not use BOTOX Cosmetic and contact Allergan (1-800-890-4345) if:

- the carton labeling does not contain an intact seal with a translucent silver Allergan logo (on both ends of the carton) or the seal has a black circle with a diagonal line through it (i.e., prohibition sign),
- the vial label does not contain a holographic film containing the name "Allergan" within rainbow colored horizontal lines, or
- the U.S. License number 1145 is not present on the vial label and carton labeling *[see How Supplied/Storage and Handling (16)]*.

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 (see Table 1). 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 for glabellar lines, 24 Units in 0.6 mL for lateral canthal lines, and 40 Units in 1 mL for forehead lines and glabellar lines. 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

Draw at least 0.5 mL (for glabellar lines), 0.6 mL (for lateral canthal lines), or 1 mL (for forehead lines treated in conjunction with glabellar lines) 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.

Glabellar Lines

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.

Inject 4 Units (0.1 mL) of reconstituted BOTOX Cosmetic 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.

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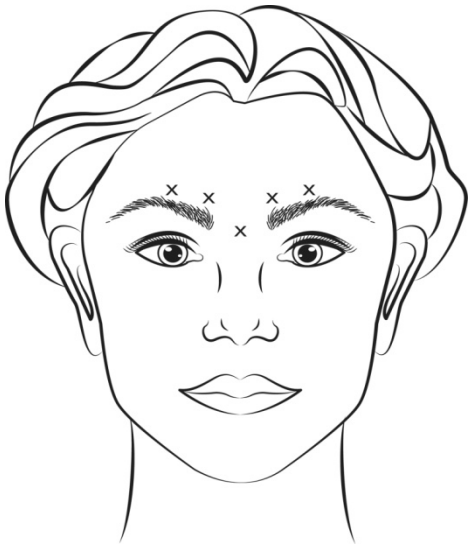
Figure 1:



Lateral Canthal Lines

Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients.

Injections should be given with the needle bevel tip up and oriented away from the eye. Inject 4 Units/0.1 mL of reconstituted BOTOX Cosmetic into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection (A) should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the lateral canthal region are above and below the lateral canthus, inject per Figure 2. Alternatively, if the lines in the lateral canthal region are primarily below the lateral canthus, inject per Figure 3.

Figure 2:

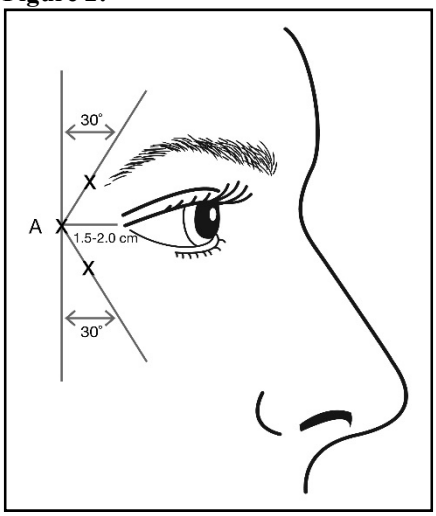
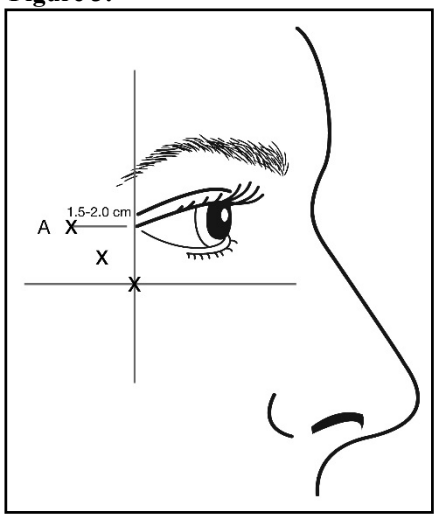


Figure 3:



For simultaneous treatment with glabellar lines, the dose is 24 Units for lateral canthal lines and 20 Units for glabellar lines (see Glabellar Lines Administration and Figure 1), with a total dose of 44 Units.

Forehead Lines

Forehead lines arise largely from the activity of the frontalis muscles. This muscle moves the brow superiorly, interacting with the procerus, orbicularis, corrugator, and depressor supercilli. Frontalis contraction causes brow elevation. The location, size, and use of the muscles vary markedly among individuals.

Treat forehead lines in conjunction with glabellar lines (see Glabellar Lines Administration and Figure 1) to minimize the potential for brow ptosis. The recommended total dose for treatment of forehead lines (20 Units [0.5 mL]) in conjunction with glabellar lines (20 Units [0.5 mL]) is 40 Units (1mL).

When identifying the location of the appropriate injection sites in the frontalis muscle, assess the overall relationship between the size of the subject's forehead, and the distribution of frontalis muscle activity.

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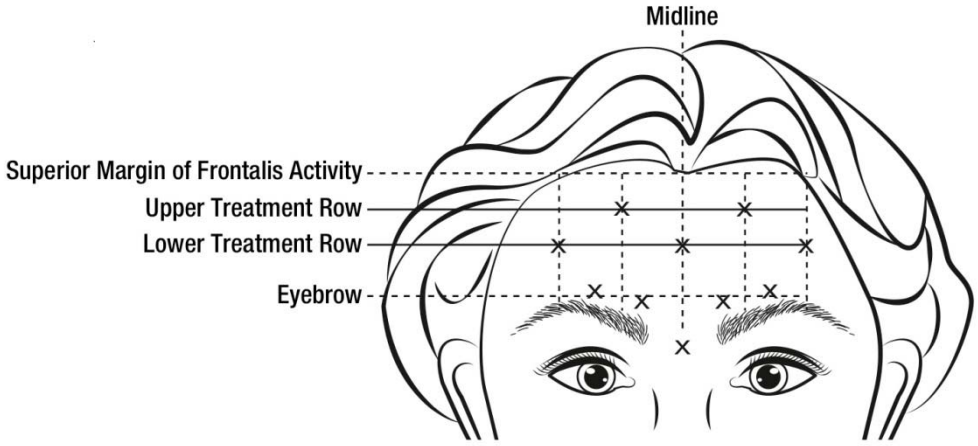
Locate the following horizontal treatment rows by light palpation of the forehead at rest and maximum eyebrow elevation:

- Superior Margin of Frontalis Activity: approximately 1 cm above the most superior forehead crease
- Lower Treatment Row: midway between the superior margin of frontalis activity and the eyebrow, at least 2 cm above the eyebrow
- Upper Treatment Row: midway between the superior margin of frontalis activity and lower treatment row

Inject 4 Units (0.1 mL) of reconstituted BOTOX Cosmetic into 5 sites in the frontalis muscle, for a total of 20 Units (0.5 mL). Place the 5 injections at the intersection of the horizontal treatment rows with the following vertical landmarks (see Figure 4):

- On the lower treatment row at the midline of the face, and 0.5 – 1.5 cm medial to the palpated temporal fusion line (temporal crest); repeat for the other side.
- On the upper treatment row, midway between the lateral and medial sites on the lower treatment row; repeat for the other side.

Figure 4:



For simultaneous treatment with lateral canthal lines, the total dose is 64 Units, comprised of 20 Units for forehead lines, 20 Units for glabellar lines, and 24 Units for lateral canthal lines (see Lateral Canthal Lines Administration and Figures 2 and 3).

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

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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 and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders 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), 24 Units (for lateral canthal lines), 40 Units (for forehead lines with glabellar lines), 44 Units (for simultaneous treatment of lateral canthal lines and glabellar lines), 64 Units (for simultaneous treatment of lateral canthal lines, glabellar lines, and forehead 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 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

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/Botox Cosmetic 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 Increased Risk of Clinically Significant Effects with 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 when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from onabotulinumtoxinA *[see Warnings and Precautions (5.2, 5.7)]*.

5.7 Dysphagia and Breathing Difficulties

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 oropharyngeal muscles that control swallowing or breathing *[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 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.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia 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)]*.

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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), ptosis, or when excessive weakness or atrophy is present in the targeted muscle(s).

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

Reduced blinking from injection of botulinum toxin products in or near the orbicularis oculi muscle can lead to corneal exposure, persistent corneal epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders.

Vigorous treatment of any corneal 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 Dry Eye in Patients Treated with BOTOX Cosmetic

There have been reports of dry eye associated with BOTOX Cosmetic injection in or near the orbicularis oculi muscle. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring patients to an ophthalmologist *[see Warnings and Precautions (5.9)]*.

5.11 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.

5.12 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

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 *[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

Table 2 lists selected adverse reactions reported by ≥1% of BOTOX Cosmetic treated subjects (N=405) 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.

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Table 2: Adverse Reactions Reported by ≥1% of BOTOX Cosmetic treated Subjects and More Frequent than in Placebo-treated Subjects in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines

Adverse Reactions by System Organ Class	BOTOX Cosmetic (N=405)	Placebo (N=130)
General Disorders and Administration Site Conditions Facial pain	6 (1%)	0 (0%)
Nervous System Disorders Facial paresis	5 (1%)	0 (0%)
Eye Disorders Eyelid ptosis	13 (3%)	0 (0%)
Musculoskeletal and Connective Tissue Disorders Muscular Weakness	6 (1%)	0 (0%)

Lateral Canthal Lines

Table 3 lists selected adverse reactions reported within 90 days following injection by ≥1% of BOTOX Cosmetic treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of BOTOX Cosmetic in the improvement of the appearance of lateral canthal lines alone.

Table 3: Adverse Reaction Reported by ≥1% of BOTOX Cosmetic treated Subjects and More Frequent than in Placebo-treated Subjects Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Lateral Canthal Lines

Adverse Reactions by System Organ Class	BOTOX Cosmetic 24 Units (N=526)	Placebo (N=530)
Eye disorders Eyelid edema	5 (1%)	0 (0%)

Forehead Lines

Table 4 lists selected adverse reactions reported by ≥1% of BOTOX Cosmetic treated subjects (N=665) aged 18 to 77 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of BOTOX Cosmetic in the improvement of the appearance of forehead lines with glabellar lines.

Table 4: Adverse Reactions Reported by ≥1% of BOTOX Cosmetic treated Subjects and More Frequent than in Placebo-treated Subjects, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Forehead Lines

Adverse Reactions by System Organ Class	BOTOX Cosmetic (20 Units forehead lines with 20 Units glabellar lines) (N=665)	Placebo (N=315)
Nervous System Disorders Headache	58 (9%)	17 (5%)
Eye Disorders Eyelid ptosis	12 (2%)	1 (0%)
Skin and Subcutaneous Tissue Disorders Brow ptosis Skin tightness	 13 (2%) 10 (2%)	 0 (0%) 0 (0%)

There were no additional adverse drug reactions reported with the simultaneous treatment of forehead lines, glabellar lines, and lateral canthal lines.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. 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 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. 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.

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with BOTOX Cosmetic had specimens analyzed for antibody formation. Among the 916 BOTOX Cosmetic treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

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The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to BOTOX Cosmetic in a mouse protection assay.

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 with the lowest effective dose given at the longest feasible intervals between injections.

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; dry eye; lagophthalmos; 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
Localized muscle twitching/involuntary muscle contractions; 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.

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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

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX Cosmetic in pregnant women.

In animal studies, administrations of BOTOX Cosmetic during pregnancy resulted in adverse effects on fetal growth (decreased fetal body weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity *[see Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated populations is unknown.

Data

Animal Data

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 4 times the average high human dose for glabellar lines, lateral canthal lines, and forehead lines of 64 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 equal the average high human dose of 64 Units based on Units/kg, and the developmental no-effect dose of 0.25 Units/kg in rabbits is 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 16 times the average high human dose of 64 Units based on Units/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of BOTOX Cosmetic in human or animal milk, the effects on the breastfed child, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BOTOX Cosmetic and any potential adverse effects on the breastfed infant from BOTOX Cosmetic or from the underlying maternal conditions.

8.4 Pediatric Use

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

8.5 Geriatric Use

Glabellar Lines

In the two initial glabellar lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older *[see Clinical Studies (14)]*.

Lateral Canthal Lines

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In the two lateral canthal lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

Forehead Lines
In the two forehead lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older.

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 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 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 pre-synaptic 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.

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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

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

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.

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 4-8 times the average high human dose for glabellar lines, lateral canthal lines, and forehead lines of 64 Units on a body weight basis (Units/kg).

14 CLINICAL STUDIES

14.1 Glabellar Lines

Two randomized, multi-center, double-blind, placebo-controlled studies of identical design were conducted to evaluate BOTOX Cosmetic for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. The studies enrolled healthy adults (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. 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 studies) or placebo (N=132, combined studies). Injection volume was 0.1 mL/injection site, for a dose/injection site in the active treatment groups of 4 Units. Subjects were injected intramuscularly in five sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units.

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

The combined results of these two efficacy studies 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 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 5), and by subject's global assessment of change in appearance of glabellar lines (Table 6).

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Table 5: 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 6: 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 7).

Table 7: 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.

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14.2 Lateral Canthal Lines

Two multicenter, randomized, double-blind, placebo-controlled studies evaluated BOTOX Cosmetic (N=833, randomized to receive any BOTOX Cosmetic treatment or N=529 randomized to receive placebo) for the temporary improvement in the appearance of moderate to severe lateral canthal lines (LCL). Study 1 assessed BOTOX Cosmetic treatment of LCL alone; Study 2 also assessed simultaneous treatment of LCL and glabellar lines (GL). Both studies enrolled healthy adults with moderate to severe LCL at maximum smile at baseline; Study 2 also required subjects to have moderate to severe GL at maximum frown at baseline.

In the 5-month Study 1, subjects were randomized to receive a single blinded treatment of 24 Units/0.6 mL (12 Units per side) consisting of 4 Units/0.1 mL into 3 sites of each orbicularis oculi muscle with either BOTOX Cosmetic (N=222) or placebo (N=223).

In the 7-month Study 2, subjects were randomized to receive either BOTOX Cosmetic in the LCL region and placebo in the GL region (24 Units; N=306), or BOTOX Cosmetic in the LCL and GL regions (44 Units [24 Units for LCL and 20 Units for GL]; N=305), or placebo in the LCL and GL regions (0 Units; N=306). Subjects received the same 24 Units regimen for LCL as in Study 1, and the labeled 20 Units (5 injections, 4 Units per site) for GL. Subjects received the same treatment at days 1 and 120.

The primary efficacy measure was the assessment of LCL severity at maximum smile using the 4-point Facial Wrinkle Scale with Photonumeric Guide (FWS; 0=none, 1= mild, 2=moderate, 3=severe). The FWS assessment was performed independently by both investigators and subjects. The primary timepoint was day 30 following the first treatment, as compared to baseline.

The primary efficacy response definition was a composite ≥2-grade improvement from baseline in LCL severity at maximum smile, assessed by both investigator and subject on a per-subject basis. For Studies 1 and 2, the proportion of responders was statistically significant favoring BOTOX Cosmetic (24 Units [LCL alone] and 44 Units [LCL and GL]) compared to placebo at day 30 (Table 8).

Table 8: Studies 1 and 2: Composite Investigator and Subject Assessment of LCL at Maximum Smile at Day 30 – Responder Rates (% and Number of Subjects Achieving ≥2-Grade Improvement from Baseline)

Study	BOTOX Cosmetic 24 Units	BOTOX Cosmetic 24 Units LCL and 20 Units GL	Placebo
Study 1	26.1% 58/222	-	1.3% 3/223
Study 2	20.3% 62/306	21.3% 65/305	0.0% 0/306

The secondary endpoint of a responder defined as achieving a grade of none or mild for Study 1 as measured by the investigator is presented in Figure 5 below.

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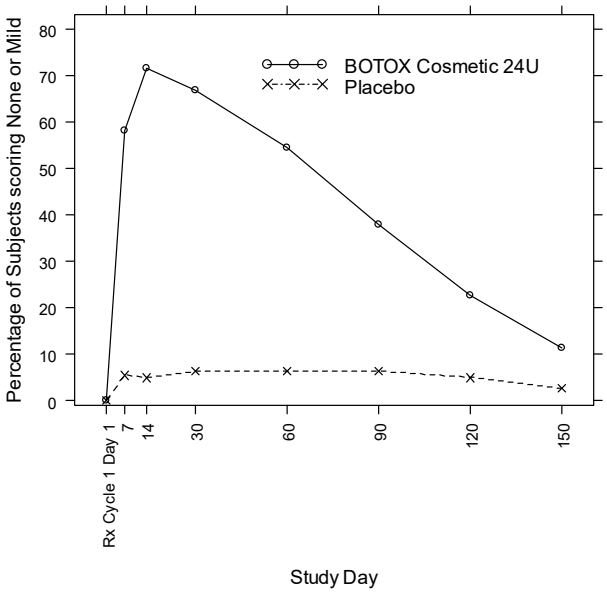
Figure 5: Percentage of Subjects with Treatment Success (% of Subjects achieving None or Mild from Baseline) by Visit (Study 1)



14.3 Forehead Lines

Two multicenter, randomized, double-blind, placebo-controlled studies evaluated BOTOX Cosmetic (N=921, randomized to receive any BOTOX Cosmetic treatment or N=257, randomized to receive placebo) for the temporary improvement in the appearance of moderate to severe forehead lines (FHL).

Study 1 assessed BOTOX Cosmetic treatment of FHL with glabellar lines (GL); Study 2 also assessed simultaneous treatment of FHL, GL, and lateral canthal lines [LCL]. Both studies enrolled healthy adults with moderate to severe FHL at maximum eyebrow elevation at baseline and moderate to severe GL at maximum frown at baseline; Study 2 also required subjects to have moderate to severe LCL at maximum smile at baseline.

In the 12-month Study 1, subjects were randomized to receive BOTOX Cosmetic 20 Units to the frontalis muscle with 20 Units to the glabellar region (for a total of 40 Units) or placebo in both areas.

In the 12-month Study 2, subjects were randomized to receive BOTOX Cosmetic 20 Units to the frontalis muscle, 20 Units to the glabellar region, and 0 Units to the LCL region (for a total of 40 units) or BOTOX Cosmetic 20 Units to the frontalis muscle, 20 Units to the glabellar region, and 24 Units to the LCL region (for a total of 64 Units) or placebo in all three areas.

The primary efficacy measure was the assessment of FHL severity at maximum eyebrow elevation using the 4-point Facial Wrinkle Scale with Photonumeric Guide (FWS; 0=none, 1= mild, 2=moderate, 3=severe). The FWS assessment was performed independently by both investigators and subjects. The primary timepoint was Day 30 following the first treatment.

The primary efficacy response definition was a composite ≥2-grade improvement from baseline in FHL severity at maximum eyebrow elevation, assessed by both investigator and subject on a per-subject basis. For Studies 1 and 2, the proportion of responders was greater in the BOTOX Cosmetic arms compared to placebo at Day 30 ($p<0.0001$ for Studies 1 and 2) (Table 9).

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Table 9: Studies 1 and 2: Composite Investigator and Subject Assessment of FHL Severity at Maximum Eyebrow Elevation at Day 30 – Responder Rates (% and Number of Subjects Achieving ≥2-Grade Improvement from Baseline)

Study	BOTOX Cosmetic (20 Units FHL with 20 Units GL)	BOTOX Cosmetic (20 Units FHL, 20 Units GL, and 24 Units LCL)	Placebo
Study 1	N=290 61%	-	N=101 0%
Study 2	N=318 46%	N=313 53%	N=156 1%

A total of 165 and 197 subjects received 3 cycles over 1 year of BOTOX Cosmetic 40 Units (20 Units FHL with 20 Units GL) and 64 Units (20 Units FHL, 20 Units GL, and 24 Units LCL), respectively. The response rate for FHL was similar across all treatment cycles.

The results for a key secondary endpoint of responders achieving a grade of none or mild on investigator ratings at maximum eyebrow elevation of FHL severity are presented below for Studies 1 and 2.

Figure 6: Percentage of Subjects with Treatment Success (Achieving None or Mild FHL from Baseline at Maximum Eyebrow Elevation) by Visit (Study 1)

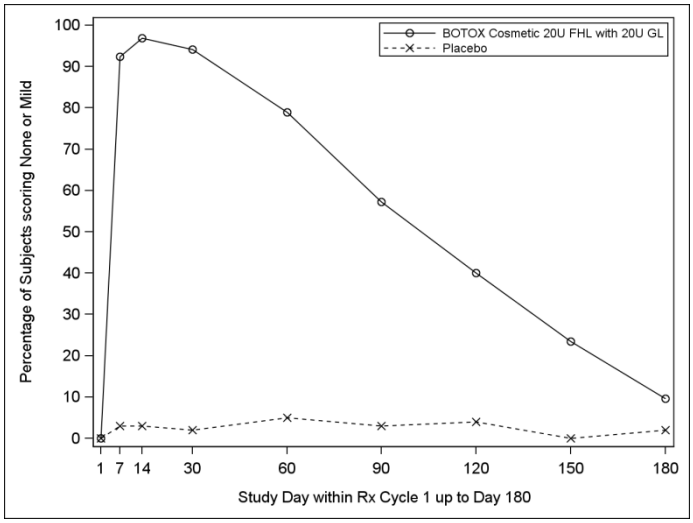

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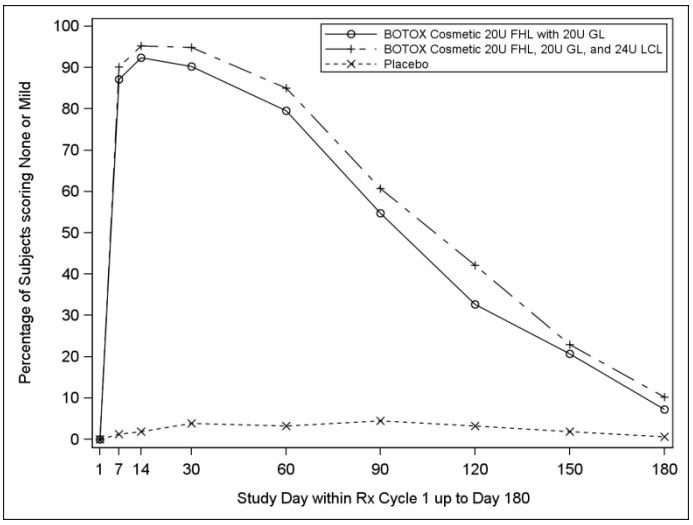
Figure 7: Percentage of Subjects with Treatment Success (Achieving None or Mild FHL from Baseline at Maximum Eyebrow Elevation) by Visit (Study 2)



The results of the Facial Line Satisfaction Questionnaire are presented in Table 10.

Table 10: Facial Lines Satisfaction Questionnaire Response Frequency at Day 60 (Percentage of Subjects)

	Study 1		Study 2	
	BOTOX Cosmetic (20 Units FHL with 20 Units GL) N=289	**Placebo N=99**	**BOTOX Cosmetic (20 Units FHL with 20 Units GL) N=317**	**Placebo N=155**
"Very satisfied"	57%	1%	35%	0%
"Mostly satisfied"	33%	0%	47%	3%
"Neither dissatisfied nor satisfied"	4%	22%	9%	23%
"Mostly dissatisfied"	4%	21%	7%	20%
"Very dissatisfied"	2%	56%	2%	54%

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX Cosmetic (onabotulinumtoxinA) for injection is a vacuum-dried powder supplied in a single-use vial in the following sizes:
50 Units: NDC 0023-3919-50
100 Units: NDC 0023-9232-01

The top and bottom flaps of the BOTOX Cosmetic cartons have a tamper-evident seal that contains a translucent silver Allergan logo and the BOTOX Cosmetic vial labels have a holographic film that contains the name "Allergan" within rainbow colored horizontal lines (rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source to see the hologram). (Note: the holographic film on the label is absent in the date/lot area.) Each BOTOX Cosmetic vial label and carton labeling also contains the U.S. License number 1145 *[see Dosage and Administration (2.1)]*.

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 if the labeling is not described as above.

Storage
Unopened vials of BOTOX Cosmetic should be stored in a refrigerator 2° to 8°C (36º to 46ºF). Do not use after the expiration date on the vial. Reconstituted BOTOX Cosmetic should be stored in a refrigerator 2° to 8°C (36º to 46ºF) and administered within 24 hours.

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.

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

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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)]*.

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.

Ophthalmic Adverse Reactions
Inform patients that Botox Cosmetic injection may cause eye dryness. Advise patients to report symptoms of eye dryness (e.g., eye pain, eye irritation, photosensitivity, or changes in vision) to their doctor.

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Madison, NJ 07940

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