Dose, dilution, reconstitution, and injection techniques

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 activity

BOTOX® Cosmetic (onabotulinumtoxinA) dose is dependent on the area(s) being treated.

BOTOX® Cosmetic dilution and reconstitution processes are the same for moderate to severe forehead lines, lateral canthal lines, and glabellar lines.

Dose[1]

- Treat forehead lines in conjunction with glabellar lines to minimize the potential for brow ptosis[1]
- The approved dose for treatment of forehead lines (20 Units) in conjunction with glabellar lines (20 Units) is 40 Units[1]
- For simultaneous treatment of all 3 areas, the dose is 20+24+20 Units (20 Units for forehead lines, 24 Units for lateral canthal lines, and 20 Units for glabellar lines) for a total dose of 64 Units[1]

40-Unit dose provides efficacy without an increase in side effects, compared with a lower dose[2]

Forehead lines	20 Units
Lateral canthal lines	24 Units
Glabellar lines	20 Units

Dilution table[1]

- BOTOX® Cosmetic is supplied in 100-Unit and 50-Unit single-use vials for reconstitution
- BOTOX® Cosmetic should be reconstituted with sterile, preservative-free 0.9% sodium chloride injection USP

Note: once open and reconstituted, use within 24 hours, because product and diluent do not contain a preservative. During the 24 hours, BOTOX® Cosmetic should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Vials are for single-use only.

DILUTION INSTRUCTIONS FOR RECONSTITUTION[1]

	Diluent added (Preservative-free 0.9% sodium chloride injection, USP only)	**Resulting dose*** (Units per 0.1 mL)
100-Unit vial	2.50 mL	4.00 Units
50-Unit vial	1.25 mL	4.00 Units

*Approved dose for forehead line treatment is 4 Units per 0.1 mL at each of the 5 injection sites (20 Units per 0.5mL) of the frontalis muscle, with 4 Units per 0.1 mL into each of 5 glabellar line sites (20 Units per 0.5mL), for a total dose of 40 Units per 1.0 mL. Approved dose for lateral canthal line treatment is 4 Units per 0.1 mL at each of the 6 injection sites (3 on each side), for a total dose of 24 Units per 0.6 mL. Approved dose for glabellar line treatment is 4 Units per 0.1 mL at each of the 5 injection sites, for a total dose of 20 Units per 0.5 mL.

BOTOX® Cosmetic (onabotulinumtoxinA) reconstitution[1]

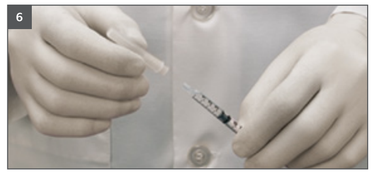
Always confirm you have received the actual BOTOX® Cosmetic (onabotulinumtoxinA) product from Allergan. Look for the holographic film on the vial label. If the rainbow lines or the name "Allergan" do not appear, please contact the Allergan Product Information Department at (800)890.4345.

Using an appropriate-sized needle and syringe, draw up 1.25 mL or 2.5 mL of preservative-free 0.9% sodium chloride injection USP (see dilution table).

Insert the needle and slowly inject the saline into the BOTOX® Cosmetic vial. Vacuum is present in the vial, which demonstrates that the sterility of the vial is intact. (If no vacuum is present, please contact Allergan directly at (800)890.4345).

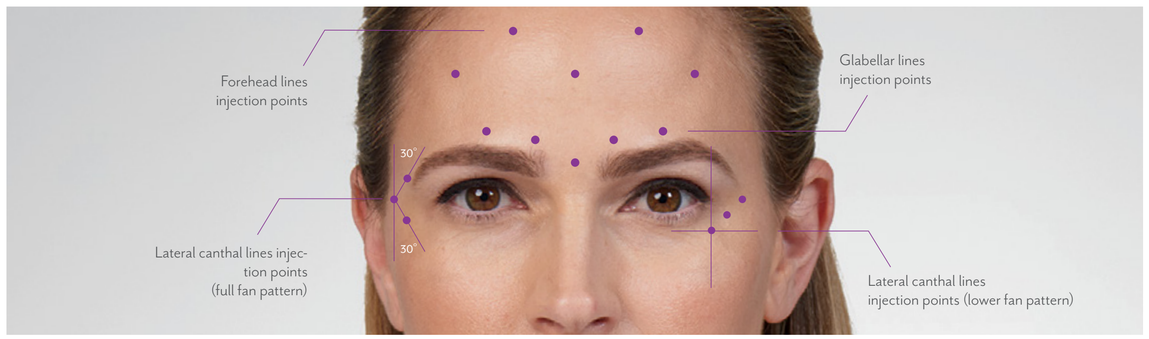
Disconnect the syringe from the needle, then gently mix BOTOX® Cosmetic with the saline by rotating the vial. Record the date and time of reconstitution in the space on the label.

Attach a new sterile syringe and draw at least 0.5 mL (for glabellar lines), 0.6 mL (for lateral canthal lines), or 1.0 mL (for forehead lines and glabellar lines) of the properly reconstituted BOTOX® Cosmetic fluid into the syringe by angling the needle into the bottom corner of the vial for full extraction. Do not completely invert the vial. Expel any air bubbles in the syringe barrel.



Disconnect the syringe from the needle used for reconstitution and attach a 30- to 33-gauge needle for injection.

BOTOX® Cosmetic injection techniques



BOTOX® Cosmetic (onabotulinumtoxinA) IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

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.

Please see full indications and additional Important Safety Information on following pages.

BOTOX® Cosmetic (onabotulinumtoxinA) Indications

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 activity

BOTOX® Cosmetic (onabotulinumtoxinA) IMPORTANT SAFETY INFORMATION (continued)

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.

BOTOX® Cosmetic
onabotulinumtoxinA injection

Injection techniques

For moderate to severe forehead lines[1]

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.

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:

- 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

For moderate to severe glabellar lines[1]

- Inject 4 Units/0.1mL into each of the 5 sites—2 in each corrugator muscle and 1 in the procerus muscle—for a total dose of 20 Units[1]

To reduce the risk of ptosis:

- Avoid injection near the l*evator palpebrae superioris*, especially in those patients with larger brow-depressor complexes[1]
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge[1]
- Ensure the injected volume and dose are accurate and, where feasible, kept to a minimum[1]
- Do not inject botulinum toxin closer than 1 cm above the central eyebrow[1]

For moderate to severe lateral canthal lines[1]

- Injections should be given with the needle bevel tip up and oriented away from the eye[1]
- Inject 4 Units/0.1mL into each of the 6 sites (3 injections per side) for a total dose of 24 Units[1]

Two approved injection patterns

1. If lines are both above and below the *lateral canthus*:
   - First injection: at least 1.5 cm to 2.0 cm temporal to the *lateral canthus* and just temporal to the lateral orbital rim[1]
   - Second injection: 1.0 cm to 1.5 cm above the first injection site and at an approximate 30° angle medially[3]
   - Third injection: 1.0 cm to 1.5 cm below the first injection site and at an approximate 30° angle medially[3]
2. If lines are primarily below the *lateral canthus*:
   - First injection: at least 1.5 cm to 2.0 cm temporal to the lateral canthus and just temporal to the lateral orbital rim[1]
   - Inject along a line that angles from *antero inferior* to *super posterior*[3]
   - Ensure that the most anterior injection is lateral to a line drawn vertically from the *lateral canthus*[3]
   - Remember to keep the most inferior injection superior to the maxillary prominence[2]

WARNINGS AND PRECAUTIONS

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.

Please see additional Important Safety Information on back cover.

BOTOX® Cosmetic (onabotulinumtoxinA) IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Spread of Toxin Effect
Please refer to Boxed Warning for Distant Spread of Toxin Effect.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of 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), and 64 Units (for simultaneous treatment of lateral canthal lines, glabellar lines, and forehead lines) have been reported.

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.

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 reactions occur, 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.

Cardiovascular System
There have been reports following administration of BOTOX® of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Increased Risk of Clinically Significant Effects with Pre-existing Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (eg, 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*).

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 *Boxed Warning*).

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

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.

ADVERSE REACTIONS
The most frequently reported adverse reaction following injection of BOTOX® Cosmetic for glabellar lines was eyelid ptosis (3%).

The most frequently reported adverse reaction following injection of BOTOX® Cosmetic for lateral canthal lines was eyelid edema (1%).

The most frequently reported adverse reactions following injection of BOTOX® Cosmetic for forehead lines with glabellar lines were headache (9%), brow ptosis (2%) and eyelid ptosis (2%).

DRUG INTERACTIONS
Co-administration of BOTOX® Cosmetic and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® Cosmetic may potentiate systemic anticholinergic effects.

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.

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

Please see BOTOX® Cosmetic Full Prescribing Information including Boxed Warning and Medication Guide.

References:
1. BOTOX® Cosmetic Prescribing Information, October 2017. **2.** Solish N, Rivers JK, Humphrey S et al. Efficacy and Safety of OnabotulinumtoxinA Treatment of Forehead Lines: A Multicenter, Randomized, Dose-Ranging Controlled Trial. *Dermatol Surg.* 2016 ; 42(3):410–419. **3.** Data on file, Allergan, Inc.; Clinical Study Report 191622-098 Amendment 5; April 4, 2012.