

BOTOX
COSMETIC
onabotulinumtoxinA
injection

THERE'S ONLY ONE BOTOX[®] COSMETIC

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One-of-a-kind formulation
from a unique and proprietary
manufacturing process¹⁻³

100 million vials distributed globally,
adhering to rigorous quality and safety
requirements for over 30 years³⁻⁵

BOTOX[®] Cosmetic (onabotulinumtoxinA) Important Information

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

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 and 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 additional Important Safety Information on following pages.

THE PROCESS IS THE PRODUCT¹

Even minor differences in botulinum toxin manufacturing processes can lead to variability in the final product^{1,6}

SECURE, STERILE, CONSISTENT, MONITORED



- All involved employees must be approved by US authorities to work with neurotoxin⁷
- Oversight and expertise are critical for the production of BOTOX[®] Cosmetic (onabotulinumtoxinA)



DID YOU KNOW?

Although collectively called the Hall strain, not all Hall strains are identical—Allergan uses a **proprietary Hall strain.**^{2,8}

RIGOROUS STERILITY AND QUALITY-CONTROL PRACTICES



- Testing for microbial and particulate contamination **every 4 hours, 24 hours a day**⁹
- Prior to filling, insides of vials are washed with water sanitized to “Water for Injection” standards to ensure vial sterility



200x
an hour
AIR FILTRATION

DID YOU KNOW?

Air is circulated **200 times an hour**—13 times more than air circulation in an operating room^{10,11}

CONSISTENT BOTOX[®] COSMETIC UNITS VIAL AFTER VIAL



- **The first nonanimal, cell-based assay**, pioneered by Allergan in 2011^{1,12}
- **Stringent assay testing to help assure 100 Units, 100% of the time**¹⁰



DID YOU KNOW?

100 million vials distributed globally⁴

QUALITY ASSURANCE THROUGHOUT DISTRIBUTION



- Secure, alarmed freezer storage with continuous **temperature monitoring throughout shipping** to ensure product is not compromised from plant to practice¹⁰
- Anticounterfeit hologram on every vial assures it's authentic BOTOX[®] Cosmetic



DID YOU KNOW?

Every vial is 100% visually inspected⁹

Allergan owns the BOTOX[®] Cosmetic manufacturing and distribution process from start to finish.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

BOTOX[®] Cosmetic (onabotulinumtoxinA) 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 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.

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. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech, or respiratory disorders occur.

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).

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 (eg, eye irritation, photophobia, or visual changes) persist, consider referring patients to an ophthalmologist.

Please see additional Important Safety Information on back cover.

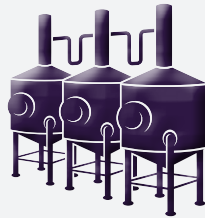
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Starting materials are different—BOTOX[®] Cosmetic has a proprietary cell bank^{2,3,8,13}



Manufacturing process is different—one-of-a-kind formulation from a unique and proprietary manufacturing process^{1-3,13}



Allergan owns end-to-end development from drug substance development to manufacturing and distribution. We stand behind BOTOX[®] Cosmetic and rigorously ensure its quality

Your practice
Our purpose

We're committed to serving you and your patients with the assurance and quality you expect.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

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 reactions following injection of BOTOX[®] Cosmetic for glabellar lines were eyelid ptosis (3%), facial pain (1%), facial paresis (1%), and muscular weakness (1%).

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.

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

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.

For more information on BOTOX[®] Cosmetic, please see accompanying full Prescribing Information including Boxed Warning and Medication Guide.

Please see additional Important Safety Information throughout this brochure.

REFERENCES: **1.** Brin MF, James C, Maltman J. Botulinum toxin type A products are not interchangeable: a review of the evidence. *Biologics*. 2014;8:227-241. **2.** Samizadeh S, De Bouille K. Botulinum neurotoxin formulations: overcoming the confusion. *Clin Cosmet Invest Dermatol*. 2018;11:273-287. **3.** BOTOX[®] Cosmetic Prescribing Information, July 2020. **4.** Data on file, Allergan, February 21, 2019; Number of Total Vials Produced at Westport. **5.** Data on file, Allergan; FDA Therapeutic Product Approval Information. **6.** Daller J. Biosimilars: a consideration of the regulations in the United States and European Union. *Regul Toxicol Pharmacol*. 2016;76:199-208. **7.** Centers for Disease Control and Prevention. Division of Select Agents and Toxins. USDA. Animal and Plant Health Inspection Service (APHIS). Agricultural Select Agent Program. Security Plan Guidance. October 2017. **8.** Fang PK, Raphael BH, Maslanka SE, Cai S, Singh BR. Analysis of genomic differences among *Clostridium botulinum* type A1 strains. *BMC Genomics*. 2010;11:725. **9.** Data on file, Allergan, November 2018; Unpublished Data—BOTOX[®] Manufacturing Process. **10.** Data on file, Allergan, 2015; Westport Manufacturing Process. **11.** Occupational Safety & Health Administration (OSHA), United States Department of Labor. Surgical suite. OSHA website. <https://www.osha.gov/SLTC/etools/hospital/surgical/surgical.html>. Accessed August 7, 2020. **12.** Allergan receives FDA approval for first-of-its-kind, fully in vitro, cell-based assay for BOTOX[®] and BOTOX[®] Cosmetic (onabotulinumtoxinA) [press release]. Irvine, CA: Allergan; June 24, 2011. <https://www.businesswire.com/news/home/20110624005918/en>. Accessed August 7, 2020. **13.** Pickett A. Botulinum toxin as a clinical product: manufacture and pharmacology. In: Foster KA, ed. *Clinical Applications of Botulinum Neurotoxin*. New York, NY: Springer+BusinessMedia; 2014:7-49. *Current Topics in Neurotoxicity*; vol 5.

