BOTOX®
onabotulinumtoxinA injection

Control that's in another class.

Reconstitution information

Indications

Bladder Dysfunction:

Overactive Bladder

BOTOX® for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity Associated With a Neurologic Condition

BOTOX® is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

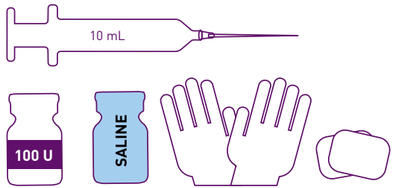
Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary 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 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 additional Important Safety Information on following pages.

Reconstitution procedure for OAB*: 100-Unit BOTOX® vial

Before beginning reconstitution, you will need:

- 100 Units of BOTOX®
  - Order an adequate supply of BOTOX® at least 2 days prior to administration
- 11 mL of sterile, nonpreserved 0.9% saline (10 mL for reconstituting BOTOX® and 1 mL for final flush)
- One 10-mL syringe and an additional syringe for 1-mL flush
- 21-gauge needle (a different injection needle will be used during the injection procedure)
- Alcohol swabs
- Sterile gloves



Note that the BOTOX® vial may appear to be empty prior to reconstitution because it contains a small amount of crystals. To determine whether you're using BOTOX®, look for a holographic film on the vial label that contains the name "Allergan" within horizontal, rainbow-colored lines.

*Overactive bladder.

IMPORTANT SAFETY INFORMATION (continued)
CONTRAINDICATIONS
BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

BOTOX® is contraindicated for intradetrusor injection in patients with a urinary tract infection; or in patients with urinary retention or post-void residual (PVR) urine volume > 200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS
Spread of Toxin Effect
See Boxed Warning.

Lack of Interchangeability Between Botulinum Toxin Products
The potency Units of BOTOX® 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® 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 following pages.

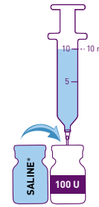
Reconstitution procedure for OAB: 100-Unit BOTOX® vial[1] (continued)

The recommended dose is 100 Units of BOTOX®

- Reconstitution of one 100-Unit vial will result in one 10-mL syringe
- The total dose is 100 Units of BOTOX® at a concentration of ≈ 10.0 Units/mL

PREPARE BOTOX® USING ASEPTIC TECHNIQUE. WIPE THE TOP OF VIALS WITH AN ALCOHOL SWAB.

1

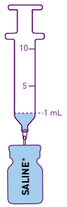


- Draw 10 mL of sterile, nonpreserved 0.9% saline into the syringe
- Inject saline into the 100-Unit BOTOX® vial. Mix gently by swirling the BOTOX® vial. Do not shake. Discard the vial if a vacuum does not pull the diluent into the vial
- BOTOX® should be administered within 24 hours after reconstitution. During this time period, unused reconstituted BOTOX® should be stored in a refrigerator (2°C-8°C) for up to 24 hours until time of use. BOTOX® vials are for single-dose only. Discard any unused portion

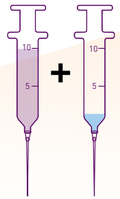
2

- Draw 10 mL of reconstituted BOTOX® from the 100-Unit BOTOX® vial into the 10-mL syringe
- Use BOTOX® immediately after reconstitution in the syringe. Do not store reconstituted BOTOX® in the syringe

3



- **In a separate syringe,** draw an additional 1 mL of saline for final flush
- **Result:** One 10-mL syringe, with 10 mL of reconstituted BOTOX® solution, at a final concentration of ≈ 10.0 Units/mL (dose of 5 Units per 0.5 mL), as well as a 1-mL syringe of saline that will be used to flush through the injection needle to deliver the small amount of BOTOX® remaining in the injection needle so that the full dose is delivered



*Unused saline should be discarded after each reconstitution procedure.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)
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.

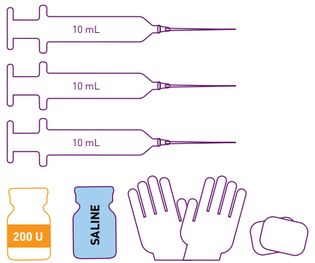
Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX® should be discontinued and appropriate medical therapy 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.

Please see additional Important Safety Information on following pages.

Reconstitution procedure for NDO*: 200-Unit BOTOX® vial

Before beginning reconstitution, you will need:

- 200 Units of BOTOX®
  – Order an adequate supply of BOTOX® at least 2 days prior to administration
- 30 mL of sterile, nonpreserved 0.9% saline and 1 mL for final flush
- Three 10-mL syringes and an additional syringe for 1 mL final flush
- 21-gauge needle (a different injection needle will be used during the injection procedure)
- Alcohol swabs
- Sterile gloves



Note that the BOTOX® vial may appear to be empty prior to reconstitution because it contains a small amount of crystals. To determine whether you're using BOTOX®, look for a holographic film on the vial label that contains the name "Allergan" within horizontal, rainbow-colored lines.

*Neurogenic detrusor overactivity.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX® (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*).

Please see additional Important Safety Information on following pages.

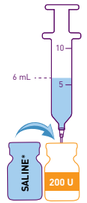
Reconstitution procedure for NDO: 200-Unit BOTOX® vial[1] (continued)

The recommended dose is 200 Units of BOTOX®

- Reconstitution of one 200-Unit vial will result in 3 syringes
- The total dose is 200 Units of BOTOX® at a concentration of ≈ 6.7 Units/mL

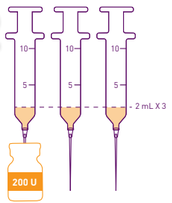
PREPARE BOTOX® USING ASEPTIC TECHNIQUE. WIPE THE TOP OF VIALS WITH AN ALCOHOL SWAB.

1



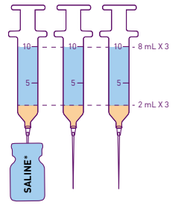
- Draw 6 mL of sterile, nonpreserved 0.9% saline into the syringe
- Inject saline into the 200-Unit BOTOX® vial. Mix gently by swirling the BOTOX® vial. Do not shake. Discard the vial if a vacuum does not pull the diluent into the vial
- Administer within 24 hours after reconstitution in the vial. During this time, reconstituted BOTOX® should be stored in a refrigerator (2°C-8°C)

2

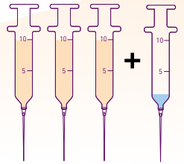


- Draw 2 mL of reconstituted BOTOX® from the 200-Unit BOTOX® vial into each of three 10-mL syringes
- Use BOTOX® immediately after reconstitution in the syringe. Do not store reconstituted BOTOX® in the syringe

3



- Draw 8 mL of sterile, nonpreserved 0.9% saline into each of the 10-mL syringes. **Mix gently**
- **In a separate syringe**, draw an additional 1 mL of saline for final flush
- **Result:** Three 10-mL syringes, with 10 mL of reconstituted BOTOX® solution per syringe, at a final concentration of ≈ 6.7 Units/mL, as well as a 1-mL syringe of saline that will be used to flush through the injection needle to deliver the small amount of BOTOX® remaining in the injection needle so that the full dose is delivered



*Unused saline should be discarded after each reconstitution procedure.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Pulmonary Effects of BOTOX® in Patients With Compromised Respiratory Status Treated for Detrusor Overactivity Associated With a Neurologic Condition
Patients with compromised respiratory status treated with BOTOX® for detrusor overactivity associated with a neurologic condition should be monitored closely.

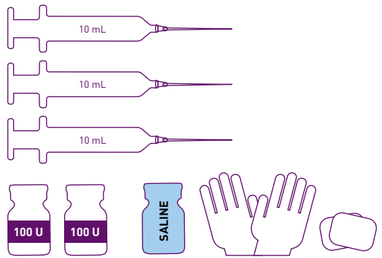
Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated With a Neurologic Condition
Autonomic dysreflexia associated with intradetrusor injections of BOTOX® could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in patients treated with BOTOX® 200 Units compared with placebo (1.5% vs 0.4%, respectively).

Please see additional Important Safety Information on following pages.

Reconstitution procedure for NDO: 2 x 100-Unit BOTOX® vials

Before beginning reconstitution, you will need:

- 2 vials of 100 Units of BOTOX®
  – Order an adequate supply of BOTOX® at least 2 days prior to administration
- 30 mL of sterile, nonpreserved 0.9% saline and 1 mL for final flush
- Three 10-mL syringes and an additional syringe for 1-mL final flush
- 21-gauge needle (a different injection needle will be used during the injection procedure)
- Alcohol swabs
- Sterile gloves



Note that the BOTOX® vial may appear to be empty prior to reconstitution because it contains a small amount of crystals. To determine whether you're using BOTOX®, look for a holographic film on the vial label that contains the name "Allergan" within horizontal, rainbow-colored lines.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Urinary Tract Infections in Patients With Overactive Bladder

BOTOX® increases the incidence of urinary tract infection. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX® for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

Urinary Retention in Patients Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

Overactive Bladder

In clinical trials, 6.5% of patients (36/552) initiated clean intermittent catheterization for urinary retention following treatment with BOTOX® 100 Units as compared to 0.4% of patients (2/542) treated with placebo. The median duration of catheterization for patients treated with BOTOX® 100 Units was 63 days (minimum 1 day to maximum 214 days) as compared to a median duration of 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

Please see additional Important Safety Information on following pages.

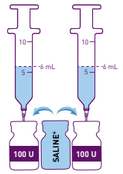
Reconstitution procedure for NDO: 2 x 100-Unit BOTOX® vials[1] (continued)

The recommended dose is 200 Units of BOTOX®

- Reconstitution of two 100-Unit vials will result in 3 syringes
- The total dose is 200 Units of BOTOX® at a concentration of ≈ 6.7 Units/mL

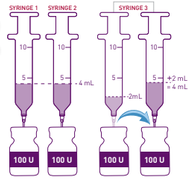
PREPARE BOTOX® USING ASEPTIC TECHNIQUE. WIPE THE TOP OF VIALS WITH AN ALCOHOL SWAB.

1



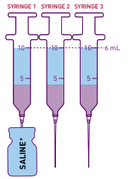
- Slowly inject 6 mL of sterile, nonpreserved 0.9% saline into each 100-Unit vial. Mix gently by swirling the BOTOX® vial. Do not shake. Discard the vial if a vacuum does not pull the diluent into the vial
- Administer within 24 hours after reconstitution in the vial. During this time, reconstituted BOTOX® should be stored in a refrigerator (2°C-8°C)

2

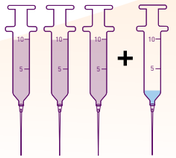


- Draw 4 mL of reconstituted BOTOX® from each 100-Unit vial into each of two 10-mL syringes
- Then draw the remaining 2 mL of reconstituted BOTOX® from each 100-Unit vial into a third 10-mL syringe
- Use BOTOX® immediately after reconstitution in the syringe. Do not store reconstituted BOTOX® in the syringe

3



- Draw 6 mL of sterile, nonpreserved 0.9% saline into each of the 10-mL syringes. **Mix gently**
- **In a separate syringe**, draw an additional 1 mL of saline for final flush
- **Result:** Three 10-mL syringes, with 10 mL of reconstituted BOTOX® solution per syringe, at a final concentration of ≈ 6.7 Units/mL, as well as a 1-mL syringe of saline that will be used to flush through the injection needle to deliver the small amount of BOTOX® remaining in the injection needle so that the full dose is delivered



*Unused saline should be discarded after each reconstitution procedure.

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Urinary Retention in Patients Treated for Bladder Dysfunction (continued)

Overactive Bladder (continued)

Patients with diabetes mellitus treated with BOTOX® were more likely to develop urinary retention than nondiabetics. In clinical trials, 12.3% of patients (10/81) with diabetes developed urinary retention following treatment with BOTOX® 100 Units vs 0% of patients (0/69) treated with placebo. In patients without diabetes, 6.3% of patients (33/526) developed urinary retention following treatment with BOTOX® 100 Units vs 0.6% of patients (3/516) treated with placebo.

Please see additional Important Safety Information on following page.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Urinary Retention in Patients Treated for Bladder Dysfunction (continued)

Detrusor Overactivity Associated With a Neurologic Condition

In clinical trials, 30.6% of patients (33/108) who were not using clean intermittent catheterization (CIC) prior to injection, required catheterization for urinary retention following treatment with BOTOX® 200 Units as compared to 6.7% of patients (7/104) treated with placebo. The median duration of postinjection catheterization for these patients treated with BOTOX® 200 Units (n = 33) was 289 days (minimum 1 day to maximum 530 days) as compared to a median duration of 358 days (minimum 2 days to maximum 379 days) for patients receiving placebo (n = 7).

Among patients not using CIC at baseline, those with multiple sclerosis were more likely to require CIC post injection than those with spinal cord injury.

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

Adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

Overactive Bladder

The most frequently reported adverse reactions for overactive bladder occurring within 12 weeks of injection include urinary tract infection (BOTOX® 18%, placebo 6%), dysuria (BOTOX® 9%, placebo 7%), urinary retention (BOTOX® 6%, placebo 0%), bacteriuria (BOTOX® 4%, placebo 2%), and residual urine volume (BOTOX® 3%, placebo 0%).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX® 100 Units and placebo than nondiabetics.

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥ 200 mL following BOTOX® injection compared to those with a maximum PVR < 200 mL following BOTOX® injection, 44% vs 23%, respectively.

Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions within 12 weeks of BOTOX® injection for detrusor overactivity associated with a neurologic condition include urinary tract infection (BOTOX® 24%, placebo 17%), urinary retention (BOTOX® 17%, placebo 3%), and hematuria (BOTOX® 4%, placebo 3%).

The following adverse event rates were reported at any time following initial injection and prior to reinjection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

Postmarketing Experience

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. 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. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Co-administration of BOTOX® and other agents interfering with neuromuscular transmission (eg, aminoglycosides, 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® 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®.

Please see BOTOX® full Prescribing Information, including Boxed Warning and Medication Guide.

Reference: 1. BOTOX® Prescribing Information, October 2019.

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