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, 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 additional Important Safety Information on the following pages.
Reconstitution procedure for OAB: 100-Unit BOTOX® vial

Before beginning reconstitution, you will need:

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

Important Safety Information (continued)

Contraindications

- BOTOX® is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection
- BOTOX® is contraindicated in patients with urinary incontinence and in patients with post-void residual

Warnings and Precautions

- Lack of interchangeability between Botox and Botox
- The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with any other botulinum toxin products and, therefore, Units of other botulinum toxin products assessed with any other specific assay method
- Spread of Toxin Effect
- Severe back pain
- Please see additional Important Safety Information on the following pages

Reconstitution procedure for OAB: 100-Unit BOTOX® vial

The recommended dose is 100 Units of BOTOX®

- Reconstitution of one 100-Unit vial
- 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
2. Inject saline into the 100-Unit BOTOX® vial. Mix gently by swirling the BOTOX® vial. Do not shake.
3. Discard the vial if a vacuum does not pull the saline into the vial
4. 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.
5. In a separate syringe, draw an additional 1 mL of saline for final flush
6. 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

Important Safety Information (continued)

Warnings and Precautions

- Severe back pain
- Please see additional Important Safety Information on the following pages

Note that the BOTOX® vial may appear to be empty prior to reconstitution because it contains a small amount of crystals. To determine whether vials of BOTOX® look for a holographic film on the vial label that contains the name "Allergan" within horizontal, rainbow-colored lines. If the vial has a vacuum and a holographic film, look for a holographic film on the vial label that contains the name "Allergan". If the vial appears to be empty prior to reconstitution because it contains a small amount of crystals, do not discard the vial and proceed with reconstitution. If a vacuum does not pull the saline into the vial, discard the vial and proceed with reconstitution.
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.”

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders

Individuals with pre-existing neuromuscular 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, dysphagia, severe dyspnea, and respiratory compromise from therapeutic doses of BOTOX® (see Warnings and Precautions).

Dysphagia and Breathing Difficulties

Treat patients with dysphagia and breathing difficulties using standard therapeutic measures. If these conditions persist, refer patients to a specialist for additional evaluation and management. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in swallowing or breathing (see boxed warning).

Please see additional Important Safety Information on the following pages.

Reconstitution procedure for NDO: 200-Unit BOTOX® vial

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

2. Inject saline into the 200-Unit BOTOX® vial. Mix gently by swirling the BOTOX® vial. Do not shake. Clarise that a vacuum does not pull the diluent into the vial

3. Administer within 24 hours after reconstitution in the vial. During this time, reconstituted BOTOX® should be stored in a refrigerator (2°C-8°C).

4. Draw 2 mL of reconstituted BOTOX® from the 200-Unit vial into each of three 10-mL syringes

5. Use BOTOX® immediately after reconstitution in the syringe. Do not store reconstituted BOTOX® in the syringe

6. Draw 8 mL of saline, nonpreserved 0.9% saline into each of the 10-mL syringes. Mix gently

7. In a separate syringe, draw an additional 1 mL of saline for final flush

8. Result: These 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

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Pulmonary Effects of BOTOX®

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. The incidence of autonomic dysreflexia was greater in patients treated with BOTOX® 200 Units compared with placebo (1.5% vs 0.4%, respectively). Patients with a neurologic condition should be monitored closely.

Please see additional Important Safety Information on the 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®
- 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
- A 21-gauge needle (a different injection needle will be used during the injection procedure)
- Alcohol swabs
- Sterile gloves

**Note:** 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 hetrographic film on the vial that contains the same “Algerian” within/nearstall, unclear-colored stain.

**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.
2. **Administer within 24 hours after reconstitution in the vial. During this time, reconstituted BOTOX® should be stored in a refrigerator (2°C-8°C).**
3. **Draw 4 mL of reconstituted BOTOX® from each 100-Unit vial into two of 10-mL syringes.** Then draw the remaining 2 mL of reconstituted BOTOX® from each 100-Unit vial into a third 10-mL syringe.
4. **Use BOTOX® immediately after reconstitution in the syringe. Do not store reconstituted BOTOX® in the syringe.**

**IMPORTANT SAFETY INFORMATION (continued)**

**WARNINGS AND PRECAUTIONS (continued)**

**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 then at 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, instituted catheterization (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.

**Urinary Retention in Patients with Overactive Bladder**

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

In clinical trials, 12.3% of patients (10/81) with diabetes developed urinary retention following treatment with BOTOX® 100 Units vs. 1.0% of patients (5/516) treated with placebo. In patients without diabetes, 3.1% of patients (23/732) developed urinary retention following treatment with BOTOX® 100 Units vs. 0.6% of patients (37/516) treated with placebo.

Please see additional Important Safety Information on the following page.
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 (MS) were more likely to require CIC post injection than those with spinal cord injury (SCI).

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® 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® 9%, 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® or 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 full Prescribing Information, including Boxed Warning and Medication Guide.