

Studied first-line in 3 pivotal trials

Efficacy established in 3 randomized, multicenter, double-blind, placebo-controlled studies.

OVERVIEW

STUDY 1

STUDY 2

STUDY 3

	Study 1 ^{1,2}	Study 2 ^{1,3}	Study 3 ^{1,4}
Number of Patients	N = 126 BOTOX® (n = 64) Placebo (n = 62)	N = 91 BOTOX® (n = 65) Placebo (n = 26)	N = 88 BOTOX® (n = 69) Placebo (n = 19)
Double-Blind Period	12 weeks	24 weeks	12 weeks
% Patients Naïve for Systemic Muscle Relaxants	87%	73%	70%
BOTOX® Dosage	200 Units to 240 Units	360 Units (n = 21) to 180 Units (n = 23) to 90 Units (n = 21)	360 Units (n = 22) to 180 Units (n = 21) to 90 Units (n = 23)
Primary End Point	Ashworth Scale score at 6 weeks (wrist)	Expanded Ashworth Scale score at 6 weeks (wrist)	Expanded Ashworth Scale score at 4 weeks (elbow, wrist)

BOTOX® is recommended as a first-line option for focal upper limb spasticity (ULS)

Botulinum neurotoxin is recommended with Level A evidence by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology as a treatment option to reduce muscle tone⁴

Efficacy End Points

- Ashworth Scale = A clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (ie,

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improvement in spasticity). Scores range from 0 (no increase in muscle tone) to 4 (limb rigid in flexion or extension)⁵

- Physician Global Assessment = Evaluates the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to + 4 = very marked improvement⁵
- The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

[Patient Profile #1 >](#)

BOTOX[®] (onabotulinumtoxinA) Important Information

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 at lower doses.

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[®] for injection 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.

Chronic Migraine

BOTOX[®] for injection is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Important Limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

Upper Limb Spasticity

BOTOX[®] for injection is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Important Limitations

Safety and effectiveness of BOTOX[®] have not been established for the treatment of other upper limb muscle groups, or for the treatment of lower limb spasticity. Safety and effectiveness of BOTOX[®] have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX[®] has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX[®] is not intended to substitute for usual standard of care rehabilitation regimens.

Cervical Dystonia

BOTOX[®] is indicated for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

Blepharospasm and Strabismus

BOTOX[®] is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

Primary Axillary Hyperhidrosis

BOTOX[®] is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Important Limitations

The safety and effectiveness of BOTOX[®] for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX[®] for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX[®] have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

BOTOX[®] 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.

Intradetrusor injection of BOTOX[®] is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection (UTI). Intradetrusor injection of BOTOX[®] is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200mL, who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS

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.

Spread of Toxin Effect

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of BOTOX[®] at the labeled dose of 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.

Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX[®] injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. (Safety and effectiveness have not been established for indications pertaining to these injection sites.) Pneumothorax associated with injection procedure has been reported following the administration of BOTOX[®] near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

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.

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

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. When distant effects occur, additional respiratory muscles may be involved (see Boxed Warning).

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from therapeutic doses of BOTOX[®].

Pulmonary Effects of BOTOX[®] in Patients With Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated With a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX[®] for upper limb spasticity or detrusor overactivity associated with a neurologic condition should be monitored closely.

Corneal Exposure and Ulceration in Patients Treated With BOTOX[®] for Blepharospasm

Reduced blinking from BOTOX[®] injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders.

Retrolbulbar Hemorrhages in Patients Treated With BOTOX[®] for Strabismus

During the administration of BOTOX[®] for the treatment of strabismus, retrolbulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX[®] (3% at 251-360 Units total dose) compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX[®] (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%).

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% versus 0.4%, respectively).

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 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

Patients with diabetes mellitus treated with BOTOX[®] were more likely to develop urinary retention than non-diabetics. In clinical trials, 12.3% of patients (10/81) with diabetes developed urinary retention following treatment with BOTOX[®] 100 Units vs. 0% 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.

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 post-injection 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 358 days (minimum 2 days to maximum 379 days) for patients receiving placebo (n=7).

Among patients not using CIC at baseline, those with MS were more likely to require CIC post-injection than those with 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. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

The following adverse reactions to BOTOX[®] for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning); Hypersensitivity Reactions (see *Contraindications and Warnings and Precautions*); Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia (see *Warnings and Precautions*); Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity (see *Warnings and Precautions*) and Urinary Retention in Patients treated for Bladder Dysfunction (see *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 non-diabetics.

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume \geq 200 mL following BOTOX[®] injection compared to those with a maximum PVR <200 mL following BOTOX[®] injection, 44% versus 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%).

Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX[®] for chronic migraine include neck pain (9%), headache (5%), eyelid ptosis (4%), migraine (4%), muscular weakness (4%), musculoskeletal stiffness (4%), bronchitis (3%), injection-site pain (3%), musculoskeletal pain (3%), myalgia (3%), facial paresis (2%), hypertension (2%), and muscle spasms (2%).

Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX[®] for upper limb spasticity include pain in extremity, muscle weakness, fatigue, nausea, and bronchitis.

Cervical Dystonia

The most frequently reported adverse reactions following injection of BOTOX[®] for cervical dystonia include dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Blepharospasm

The most frequently reported adverse reactions following injection of BOTOX[®] for blepharospasm include ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Strabismus

The most frequently reported adverse events following injection of BOTOX[®] for strabismus include ptosis (15.7%) and vertical deviation (16.9%).

Primary Axillary Hyperhidrosis

The most frequently reported adverse events (3%-10% of adult patients) following injection of BOTOX[®] for severe primary axillary hyperhidrosis include injection-site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

Post Marketing Experience

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 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. 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](#).

References: 1. Data on file, Allergan, Inc.; Clinical Study Report 191622. 2. Data on file, Allergan, Inc.; Clinical Study Report 133/134. 3. Data on file, Allergan, Inc.; Clinical Study Report 418/422. 4. Simpson DM, Gracies J-M, Graham HK, et al; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(19):1691-1698 5. BOTOX[®] Prescribing Information, January 2013.

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