History of BOTOX®
(onabotulinumtoxinA)

BOTOX® (onabotulinumtoxinA) & BOTOX® Cosmetic (onabotulinumtoxinA) Important Information

IMPORTANT SAFETY INFORMATION
BOTOX® and BOTOX® Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX® or BOTOX® Cosmetic:

- **Problems swallowing, speaking, or breathing,** due to weakening of associated muscles, can be severe and result in loss of life. You are at the highest risk if these problems are pre-existing before injection. Swallowing problems may last for several months
- **Spread of toxin effects.** The effect of botulinum toxin may affect areas away from the injection site and cause serious symptoms including: loss of strength and all-over muscle weakness, double vision, blurred vision and drooping eyelids, hoarseness or change or loss of voice (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing. **If this happens, do not drive a car, operate machinery, or do other dangerous activities**

There has not been a confirmed serious case of spread of toxin effect away from the injection site when BOTOX® has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, strabismus, or when BOTOX® Cosmetic has been used at the recommended dose to treat frown lines or crow's feet lines.

Indications
BOTOX® is a prescription medicine that is injected into muscles and used:

Please see additional Important Information on the following pages.

Botulinum toxin, a purified protein derived from the bacterium *Clostridium botulinum*, has been researched for more than 100 years. Ever since the bacterium was identified in 1895, researchers have been intrigued by its potential therapeutic uses.

BOTOX® (onabotulinumtoxinA) is one of seven distinct botulinum toxin strains produced from the *Clostridium botulinum* bacterium, which includes types A, B, C, D, E, F, G, and H.[1,2] BOTOX® is a prescription medicine which contains tiny amounts of the highly purified botulinum toxin protein refined from the bacterium. The product is administered in small therapeutic doses by intramuscular or intradermal injections directly into the affected area, depending on the indication, producing a temporary decrease of muscle or gland activity.

The therapeutic effect of BOTOX® is temporary and usually lasts between three to ten months, depending on the approved indication and on the individual patient. Over time the nerve inhibition produced by BOTOX® neurotoxin is reversed as nerve endings recover and begin to release acetylcholine again, at which time another injection of BOTOX® may be needed to maintain therapeutic effect.

UNITED STATES APPROVAL MILESTONES

- **1989:** The therapeutic value of botulinum toxin type A is recognized when Oculinum, Inc. receives one of the first approvals by the U.S. Food and Drug Administration (FDA) in December 1989 under the newly established orphan drug status to market *Oculinum* in the United States for the treatment of two eye muscle disorders –

BOTOX® (onabotulinumtoxinA) & BOTOX® Cosmetic (onabotulinumtoxinA) Important Information (continued)

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults 18 years and older when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults 18 years and older with overactive bladder due to neurologic disease who still have leakage or cannot tolerate the side effects after trying an anticholinergic medication
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day in people 18 years or older
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in people 18 years and older with upper limb spasticity
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in people 16 years and older
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older

BOTOX® is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough in people 18 years and older.

BOTOX® Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary).

BOTOX® Cosmetic is a prescription medicine that is injected into the area around the side of the eyes to improve the look of moderate to severe crow's feet lines in adults for a short period of time (temporary).

It is not known whether BOTOX® and BOTOX® Cosmetic are safe or effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine).

Please see additional Important Safety Information on the following pages.

strabismus (a disorder where the eyes do not line up in the same direction) and **blepharospasm** (involuntary spasms of the eyelids) in people 12 years and older. Shortly after, Allergan acquires Oculinum, Inc. and receives FDA approval to change the product's name to BOTOX® (botulinum toxin type A) or BOTOX® (onabotulinumtoxinA) as it is now known.[3]

- **2000:** In December 2000, the FDA approves BOTOX® for the treatment of abnormal head position and neck pain that happens with **cervical dystonia (CD)** in people 16 years and older.[3]

- **2002:** In April 2002, Allergan receives FDA approval to market the same formulation – under the name BOTOX® Cosmetic (onabotulinumtoxinA) – with dosing specific to temporarily improve the appearance of moderate to severe frown lines between the eyebrows (**glabellar lines**) in people 18 to 65 years of age.[3]

- **2004:** In July 2004, BOTOX® is granted approval by the FDA to treat the symptoms of severe underarm sweating (**severe primary axillary hyperhidrosis**) in people 18 years and older when medicines used on the skin (topical) do not work well enough. It is not known whether BOTOX® is safe or effective for severe sweating anywhere other than the armpits.[3]

- **2010:** In March 2010, BOTOX® is granted FDA approval for the treatment of increased muscle stiffness in the elbow, wrist and finger muscles in people 18 years and older with **upper limb spasticity**. It is not known whether BOTOX® is safe or effective to treat increased stiffness in upper-limb muscles other than those in the elbow, wrist and fingers, or to treat increased stiffness in the lower-limb muscles. BOTOX® has not been shown

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

It is not known whether BOTOX® is safe or effective to treat increased stiffness in upper-limb muscles other than those in the elbow, wrist, and fingers, or to treat increased stiffness in lower-limb muscles. BOTOX® has not been shown to help people perform task-specific functions with their upper limbs or increase movement in joints that are permanently fixed in position by stiff muscles. Treatment with BOTOX® is not meant to replace your existing physical therapy or other rehabilitation that your doctor may have prescribed.

It is not known whether BOTOX® and BOTOX® Cosmetic are safe or effective for severe sweating anywhere other than your armpits.

Do not take BOTOX® or BOTOX® Cosmetic if you: are allergic to any of the ingredients in BOTOX® (see Medication Guide for ingredients); had an allergic reaction to any other botulinum toxin product such as *Myobloc®* (rimabotulinumtoxinB), *Dysport®* (abobotulinumtoxinA), or *Xeomin®* (incobotulinumtoxinA); have a skin infection at the planned injection site.

Do not take BOTOX® for the treatment of urinary incontinence if you: have a urinary tract infection (UTI) or cannot empty your bladder on your own and are not routinely catheterizing.

Due to the risk of urinary retention (not being able to empty the bladder), only patients who are willing and able to initiate catheterization post-treatment, if required, should be considered for treatment.

Patients treated for 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 these 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.

Please see additional Important Safety Information on the following pages.

to help people perform task-specific functions of their upper limbs or increase movement in joints that are permanently fixed in position by stiff muscles. Treatment with BOTOX® (onabotulinumtoxinA) is not meant to replace a patient's existing physical therapy or other rehabilitation that the doctor may have prescribed.[3]

In October 2010, BOTOX® receives FDA approval to prevent headaches in adults with **chronic migraine** who have 15 or more headache days each month with headaches lasting four hours or more each day in people 18 years or older. It is not known whether BOTOX® is safe or effective to prevent headaches in patients with migraine who have 14 or fewer headache days each month (episodic migraine).[3]

- **2011:** In August 2011, Allergan receives FDA approval for BOTOX® to treat leakage of urine (incontinence) in adults 18 years or older with **overactive bladder due to a neurologic disease** who still have leakage or experience too many side effects after trying an anticholinergic medication.[3]

- **2013:** In January 2013, the FDA approves BOTOX® to treat **overactive bladder** symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults 18 years and older when another type of medicine (anticholinergic) does not work well enough or cannot be taken.[4]

In September 2013, Allergan receives approval for BOTOX® Cosmetic (onabotulinumtoxinA) to temporarily improve the appearance of moderate to severe **lateral canthal lines** (most commonly known as crow's feet lines) in adults. BOTOX® Cosmetic is the only pharmaceutical product of its kind to be approved for the temporary improvement in the appearance of both moderate to severe glabellar lines and crow's feet lines in adults in the United States.[5]

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

Patients with diabetes mellitus treated with BOTOX® were more likely to develop urinary retention than non-diabetics.

Patients treated for overactive bladder due to neurologic disease
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.

The dose of BOTOX® and BOTOX® Cosmetic is not the same as, or comparable to, any other botulinum toxin product.

Serious and/or immediate allergic reactions have been reported. These reactions include itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you experience any such symptoms; further injection of BOTOX® or BOTOX® Cosmetic should be discontinued.

Tell your doctor about all your muscle or nerve conditions such as amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), myasthenia gravis, or Lambert-Eaton syndrome, as you may be at increased risk of serious side effects including severe dysphagia (difficulty swallowing) and respiratory compromise (difficulty breathing) from typical doses of BOTOX® or BOTOX® Cosmetic.

Please see additional Important Safety Information on the following page.

ABOUT BOTOX®

Since its first approval in 1989, BOTOX® (onabotulinumtoxinA) has been recognized by regulatory authorities worldwide as an effective treatment of 27 different indications in approximately 88 countries, benefiting patients worldwide.[6]

BOTOX® is one of the most widely researched medicines in the world with approximately 2,800 articles on BOTOX® and BOTOX® Cosmetic (onabotulinumtoxinA) published in scientific and medical journals.[7]

Today, Allergan is working in collaboration with many academic institutions, researchers, scientists and physicians to continue exploring the full therapeutic potential of this versatile medicine and to develop new medical uses for BOTOX® in other areas where there is a need for new treatment options.

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

Tell your doctor if you have any breathing-related problems. Your doctor will want to monitor you for any breathing problems during your treatment with BOTOX® for upper limb spasticity or for detrusor overactivity associated with a neurologic condition. The risk of pulmonary effects in patients with compromised respiratory status is increased in patients receiving BOTOX®.

Cornea problems have been reported. Cornea (surface of the eye) problems have been reported in some people receiving BOTOX® for their blepharospasm, especially in people with certain nerve disorders. BOTOX® may cause the eyelids to blink less, which could lead to the surface of the eye being exposed to air more than is usual. Tell your doctor if you experience any problems with your eyes while receiving BOTOX®. Your doctor may treat your eyes with drops, ointments, contact lenses, or with an eye patch.

Bleeding behind the eye has been reported. Bleeding behind the eyeball has been reported in some people receiving BOTOX® for their strabismus. Tell your doctor if you notice any new visual problems while receiving BOTOX®.

Bronchitis and upper respiratory tract infections (common colds) have been reported. Bronchitis was reported more frequently in people receiving BOTOX® for their upper limb spasticity. Upper respiratory infections (common colds) were also reported more frequently in people with prior breathing-related problems.

Autonomic dysreflexia in patients treated for overactive bladder due to neurologic disease
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).

Tell your doctor about all your medical conditions, including if you: have or have had bleeding problems; have plans to have surgery; had surgery on your face; weakness of forehead muscles, such as trouble raising your eyebrows; drooping eyelids; any other abnormal facial change; have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever; have problems emptying your bladder on your own and are being treated for urinary incontinence; are pregnant or plan to become pregnant (it is not known if BOTOX® or BOTOX® Cosmetic can harm your unborn baby); are breastfeeding or plan to breastfeed (it is not known if BOTOX® or BOTOX® Cosmetic passes into breast milk).

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal products. Using BOTOX® or BOTOX® Cosmetic with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX® or BOTOX® Cosmetic in the past.**

Especially tell your doctor if you: have received any other botulinum toxin product in the last 4 months; have received injections of botulinum toxin such as *Myobloc®*, *Dysport®*, or *Xeomin®* in the past (be sure your doctor knows exactly which product you received); have recently received an antibiotic by injection; take muscle relaxants; take an allergy or cold medicine; take a sleep medicine; take anti-platelets (aspirin-like products) or anticoagulants (blood thinners).

Other side effects of BOTOX® and BOTOX® Cosmetic include: dry mouth, discomfort or pain at the injection site, tiredness, headache, neck pain, and eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes. In people being treated for urinary incontinence other side effects include: urinary tract infection, painful urination, and/or inability to empty your bladder on your own. If you have difficulty fully emptying your bladder after receiving BOTOX® , you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.

For more information refer to the Medication Guide or talk with your doctor.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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

For further information, please contact Allergan, Inc.'s Corporate Affairs & Public Relations Department at +1 (714) 246-4819

Myobloc® is a registered trademark of Solstice Neuroscience, Inc.
Dysport® is a registered trademark of Ipsen Biopharm, Ltd.
Xeomin® is a registered trademark of Merz Pharma Gmbh & Co.

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