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 –
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

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

**Please see additional Important Safety Information on the following pages.**
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](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

REFERENCES:


4. BOTOX® (onabotulinumtoxinA) Prescribing Information, February 2014

5. BOTOX® (onabotulinumtoxinA) Cosmetic Prescribing Information, September 2013

6. Allergan data on file

7. Allergan data on file; Global Literature & Information Services and Global Regulatory Affairs