



HISTORY AND DEVELOPMENT

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

Seven distinct antigenic botulinum toxins are produced by different strains of the *Clostridium botulinum* (A, B, C, D, E, F and G). OnabotulinumtoxinA (BOTOX[®]) is a medical product containing tiny amounts of the highly purified botulinum toxin protein refined from the bacterium. The product is administered in small injections to reduce specific muscle activity by blocking the overactive nerve impulses that trigger excessive muscle contractions or glandular activity.

Over the past 20 years, BOTOX[®] neurotoxin has been approved in approximately 80 countries for 21 different indications, benefiting patients worldwide. Additionally, the same formulation with dosing specific to moderate to severe glabellar lines was approved in 2002 as BOTOX[®] Cosmetic (onabotulinumtoxinA).

Indications

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

- To treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- 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.

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).

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 after treatment with BOTOX[®] or BOTOX[®] Cosmetic:

- **Problems swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of BOTOX[®] or BOTOX[®] Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with BOTOX[®] or BOTOX[®] Cosmetic.

Please see next page for additional Important Safety Information.



In the United States, BOTOX[®] (onabotulinumtoxinA) therapy was granted approval in 1989 by the U.S. Food and Drug Administration (FDA) to treat certain types of eye muscle problems (strabismus) and abnormal spasm of the eyelids (blepharospasm) in people 12 years and older. In December 2000, BOTOX[®] was approved by the FDA for the treatment of the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults. In April 2002, the same formulation of BOTOX[®] neurotoxin received approval by the FDA under the name BOTOX[®] Cosmetic (onabotulinumtoxinA), with dosing specifically 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). Most recently, in July 2004, BOTOX[®] was granted approval in the United States to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

HISTORICAL TIMELINE

1895

The bacterium *Bacillus botulinum* (later renamed *Clostridium botulinum*) was identified by Prof. Emile Pierre van Ermengem, of Ellezelles, Belgium.

1920s

Botulinum Toxin Type A was isolated in purified form as a stable acid precipitate by Herman Sommer, M.D., at the University of California, San Francisco.

1946

Edward J. Schantz, Ph.D., and colleagues succeeded in purifying Botulinum Toxin Type A in crystalline form, for the first time providing scientists with the raw material necessary to study the molecule in greater detail.

IMPORTANT SAFETY INFORMATION (continued)

Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX[®] or BOTOX[®] Cosmetic:

- Swallowing problems may last for several months. People who already have swallowing or breathing problems before receiving BOTOX[®] or BOTOX[®] Cosmetic have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause

symptoms of a serious condition called botulism. The symptoms of botulism include: loss of strength and muscle weakness all over the body, 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.

These symptoms can happen hours to weeks after you receive an injection of BOTOX[®] or BOTOX[®] Cosmetic.

Please see next page for additional Important Safety Information.

1950s

The first important studies with Botulinum Toxin Type A yielded major results when researcher Vernon Brooks, M.D. discovered that botulinum toxin, when injected into a hyperactive muscle, blocks the release of acetylcholine from motor nerve endings, thus inducing a temporary reduction in the targeted muscle's activity. This breakthrough sparked new interest in Botulinum Toxin Type A as a potentially significant therapeutic agent.

1960s and 1970s

Research into the role of Botulinum Toxin Type A in muscle disorders accelerated in the late 1960s, when Alan B. Scott, M.D., of the Smith-Kettlewell Eye Research Foundation in San Francisco, initiated animal studies with Botulinum Toxin Type A. Dr. Scott hypothesized that the drug might be an effective therapy for strabismus (crossed eyes), a type of "ophthalmic dystonia," and an alternative to surgery, then the only effective intervention. Dr. Scott discovered that by injecting a small amount of botulinum toxin into the hyperactive ocular muscles in monkeys he was able to realign crossed eyes associated with strabismus.

For the next 20 years, Dr. Scott collaborated with Dr. Schantz to develop Botulinum Toxin Type A for human treatment. In the late 1970s, Dr. Scott formed his own company, Oculinum, Inc., where he continued to study botulinum toxin type in human volunteers.

1988

Allergan, Inc. acquired the rights to distribute Dr. Scott's Botulinum Toxin Type A product, *Oculinum*.

1989

The therapeutic value of Botulinum Toxin Type A to address an unmet medical need was recognized when Oculinum, Inc. received one of the first approvals by the U.S. Food and Drug Administration (FDA) under the newly established orphan drug status to market *Oculinum* in the United States for the treatment of strabismus

IMPORTANT SAFETY INFORMATION (continued)

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving BOTOX® or BOTOX® Cosmetic" in Medication Guide.

There has not been a confirmed serious case of spread of toxin effect away from the injection site when BOTOX® (onabotulinumtoxinA) has been used at the recommended dose to treat severe underarm sweating, blepharospasm, or strabismus,

or when BOTOX® Cosmetic (onabotulinumtoxinA) has been used at the recommended dose to treat frown lines.

Tell your doctor about all your medical conditions, including if you have: a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome).

Please see next page for additional Important Safety Information.



and blepharospasm (uncontrollable eye blinking) in people 12 years and older. Shortly after, Allergan acquired Oculinum, Inc. and received FDA approval to change the product's name to BOTOX[®] (Botulinum Toxin Type A), which was recently changed to BOTOX[®] (onabotulinumtoxinA).

2000

The FDA approved BOTOX[®] for the treatment of the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.

2002

Allergan received FDA approval to market the same formulation 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). With the new license, the product is marketed as BOTOX[®] Cosmetic (onabotulinumtoxinA) in the United States, with dosing specific to temporarily treat frown lines between the brows.

2004

Most recently, in July 2004, BOTOX[®] neurotoxin was granted approval in the United States to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

2009

The year 2009 marks the 20th Anniversary of the first FDA approval of BOTOX[®] neurotoxin. Over the past 20 years, BOTOX[®] has been recognized by regulatory authorities worldwide as an effective treatment for 21 different medical uses in approximately 80 countries.

IMPORTANT SAFETY INFORMATION (continued)

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products.

BOTOX[®] or BOTOX[®] Cosmetic can cause serious side effects. 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. Symptoms of an allergic reaction to BOTOX[®] and BOTOX[®] Cosmetic may 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 are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of BOTOX[®] and BOTOX[®] Cosmetic. For more information, ask your doctor or pharmacist.

Please see next page for additional Important Safety Information.

The Future of BOTOX®

Today, Allergan, Inc. 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. With approximately 2,000 publications on BOTOX® (onabotulinumtoxinA) and BOTOX® Cosmetic (onabotulinumtoxinA) in scientific and medical journalsⁱ, BOTOX® is one of the most widely researched medicines in the world.

IMPORTANT SAFETY INFORMATION (continued)

For additional information refer to Medication Guide. This Medication Guide summarizes the most important information about BOTOX® and BOTOX® Cosmetic. If you would like more information, talk with your doctor.

Please see the accompanying full Product Information, including Medication Guide, for BOTOX®.

Please see the accompanying full Product Information, including Medication Guide, for BOTOX® Cosmetic.

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APC54PJ09

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