



BOTOX[®] (Botulinum Toxin Type A) HISTORY AND DEVELOPMENT

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.

Seven distinct antigenic botulinum toxins are produced by different strains of the *Clostridium botulinum* (A, B, C, D, E, F and G). Botulinum Toxin Type A (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 glabellar lines was approved in 2002 as BOTOX[®] Cosmetic. In fact, BOTOX[®] neurotoxin has more approved indications worldwide than any other botulinum toxin product currently on the market.

In the United States, BOTOX[®] therapy was granted approval in 1989 by the U.S. Food and Drug Administration (FDA) for the treatment of strabismus (crossed eyes) and blepharospasm (uncontrollable eye blinking) associated with dystonia. In December 2000, BOTOX[®] was approved by the FDA for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia. In April 2002, the same formulation of BOTOX[®] neurotoxin received approval by the FDA, under the name of BOTOX[®] Cosmetic (Botulinum Toxin Type A), with dosing specifically for the temporary improvement in the appearance of moderate to severe glabellar lines (the vertical “frown lines” between the eyebrows) in adult women and men ages 18 to 65. More recently, in July 2004, BOTOX[®] was granted approval in the United States for the treatment of severe primary axillary hyperhidrosis (excessive underarm sweating) that is inadequately managed with topical agents.

Please refer to important BOTOX[®] information on page 4

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.

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.

Please refer to important BOTOX[®] information on page 4



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 and blepharospasm (uncontrollable eye blinking) associated with dystonia. Shortly after, Allergan acquired Oculinum, Inc. and received FDA approval to change the product's name to BOTOX[®] (Botulinum Toxin Type A).

2000

The FDA approved BOTOX[®] for the treatment of abnormal head position and neck pain associated with cervical dystonia in adults.

2002

Allergan received FDA approval to market the same formulation for the temporary improvement in the appearance of moderate to severe glabellar lines (the vertical "frown lines" between the brows) in adult women and men ages 18 to 65. With the new license, the product was marketed as BOTOX[®] Cosmetic (Botulinum Toxin Type A) in the United States, with dosing specific to treat frown lines between the brows.

2004

Most recently, in July 2004, BOTOX[®] neurotoxin was granted approval in the United States for the treatment of severe primary axillary hyperhidrosis (excessive underarm sweating) that is inadequately managed with topical agents.

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.

Please refer to important BOTOX[®] information on page 4



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® and BOTOX® Cosmetic in scientific and medical journalsⁱ, BOTOX® is the most widely researched neurotoxin in the world.

Important BOTOX® and BOTOX® Cosmetic (Botulinum Toxin Type A) Information

BOTOX® is approved for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia.

BOTOX® is approved 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.

The efficacy of BOTOX® treatment in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been established. BOTOX® is ineffective in chronic paralytic strabismus except when used in conjunction with surgical repair to reduce antagonist contracture.

And BOTOX® is approved for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

BOTOX® Cosmetic is approved for the temporary treatment of moderate to severe frown lines between the brows in people ages 18 – 65.

Important Safety Information

Who should not be treated with BOTOX®

BOTOX® and BOTOX® Cosmetic injections should not be given to people who have an infection where the physician proposes to inject. They should not be given to people who are known to be sensitive to any ingredient in the BOTOX® product.

Warnings

Serious heart problems and serious allergic reactions have been reported rarely. If you think you are having an allergic reaction or other reactions, such as difficulty swallowing, speaking, or breathing, call your doctor immediately. Patients with certain neuromuscular disorders such as ALS, myasthenia gravis, or Lambert-Eaton syndrome may be at increased risk of serious side effects.

Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia (difficulty swallowing) and respiratory compromise from typical doses of BOTOX®.

Continued on next page

Warnings (continued)

Dysphagia (difficulty swallowing) is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube.

Precautions

Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech, or respiratory disorders arise.

Side Effects

Localized pain, infection, inflammation, tenderness, swelling, redness and/or bruising may be associated with the injection.

In cervical dystonia, the most common side effects following injection include difficulty swallowing (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

In blepharospasm, the most common side effects following injection include ptosis (20.8%), inflammation of the cornea (6.3%), and eye dryness (6.3%).

In strabismus, the most common side effects following injection include ptosis (15.7%) and vertical deviation (16.9%).

In severe primary axillary hyperhidrosis, the most common side effects (3-10% of patients) following injection include injection-site pain and bleeding, non-underarm sweating, infection, sore throat, flu, headache, fever, neck or back pain, itching and anxiety.

The most common side effects following BOTOX[®] Cosmetic injections include temporary eyelid droop and nausea.

BOTOX[®] therapy should only be administered by a trained and qualified physician. Please see accompanying full product information for BOTOX[®] and BOTOX[®] Cosmetic, also available by visiting www.BOTOX.com and www.BOTOXCosmetic.com or by visiting www.BOTOXGlobalNews.com, selecting the country of interest and clicking on "Country Resources/Prescribing Information."

For further information please contact Allergan, Inc.:

Caroline Van Hove: 714-246-5134

Kellie Reagan: 714-246-2278

© 2009 Allergan, Inc. Irvine, CA 92612. ® marks owned by Allergan, Inc.

APC10YG09

ⁱ Allergan data on file; Global Literature & Information Services