



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 18 years, BOTOX® neurotoxin has been approved in more than 75 countries for 20 different indications to provide effective treatment to patients suffering from a range of neurological disorders. 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, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. 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. 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.

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.

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 “relaxation” of the targeted muscle. 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 and blepharospasm (uncontrollable eye blinking) associated with dystonia, including benign essential blepharospasm or VII nerve disorder in patients 12 years of age and older. 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 BOTOX[®] 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.

The Future of BOTOX[®]

In the United States, BOTOX[®] is currently being investigated for the treatment of additional medical conditions, including headache/migraine, post-stroke spasticity, and overactive bladder.

With more than 3,000¹ publications on Botulinum Toxin Type A in scientific and medical journals, BOTOX[®] is one of the most researched medicines in the world.

BOTOX[®] therapy should only be administered by a trained and qualified physician. Further product and prescribing information is available by visiting www.Botox.com or www.BotoxCosmetic.com; or by visiting www.BotoxGlobalNews.com, selecting the country of interest and clicking on “Country Resources/Prescribing Information.”

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¹ Medline search. Accessed: August 8, 2007