

## **BOTOX® (ONABOTULINUMTOXINA) RECEIVES U.S. FDA APPROVAL FOR THE TREATMENT OF URINARY INCONTINENCE IN ADULTS WITH NEUROLOGICAL CONDITIONS INCLUDING MULTIPLE SCLEROSIS AND SPINAL CORD INJURY**

*Clinical Trials Showed Approximately 20 Fewer Urinary Leaking Episodes Per Week At Week Six; BOTOX® Proven Effective Up To 10 Months In Patients Who Have An Inadequate Response To Or Are Intolerant Of An Anticholinergic Medication*

**IRVINE, Calif., August 24, 2011** -- Allergan, Inc. (NYSE:AGN) today announced the United States Food and Drug Administration (FDA) has approved BOTOX® (onabotulinumtoxinA) for injection for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g. spinal cord injury (SCI), multiple sclerosis (MS)) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.<sup>1</sup> Urinary incontinence (bladder leakage) due to detrusor (bladder muscle) overactivity in patients living with MS or SCI is a chronic condition affecting approximately 340,000 people in the United States.<sup>2</sup> Current standard of care includes oral medications that are taken regularly, known as anticholinergics; however, it is estimated that 71 percent of people stop taking at least one oral medication within 12 months.<sup>3</sup> If oral medications fail, then surgery may be considered (e.g. implanting a neuromodulation device or bladder augmentation surgery).

BOTOX® neurotoxin was studied in people living with MS and SCI with urinary incontinence due to detrusor overactivity who had an inadequate response to or who were intolerant of an anticholinergic medication. In Allergan's two Phase III clinical trials, injecting 200 units of BOTOX® directly into the bladder muscle reduced urinary incontinence episodes by approximately 20 episodes per week at week six (19.9 and 19.6 episodes/week vs. 10.6 and 10.8 for the placebo group)).<sup>4</sup> Patients in the clinical trials were considered for retreatment with BOTOX® when the clinical effect of their previous treatment wore off, which in the trials was up to 10 months (42-48 weeks for the 200U BOTOX® group vs. 13-18 weeks for the placebo group).

"Urinary incontinence due to detrusor overactivity in patients with a neurologic condition is a serious medical problem, and for people who do not respond to or cannot tolerate the side effects of an oral anticholinergic medication, BOTOX® is a new long-lasting treatment option to reduce urinary incontinence episodes and address a particularly burdensome issue," said Scott Whitcup, M.D., Allergan's Executive Vice President, Research and Development and Chief Scientific Officer. "We are proud to bring the seventh medical use of BOTOX® in the United States to market. BOTOX® is the first neurotoxin to undergo formal clinical evaluation and receive FDA approval for a urological indication. This approval of BOTOX® is an important milestone in Allergan's commitment to develop and make available novel treatment options for urologists and their patients."

People living with MS develop lesions on the spinal cord, while people who sustain a spinal cord injury have irreversible nerve damage, resulting in the inability of the spinal cord and bladder to communicate effectively. As a result, the bladder muscle involuntarily contracts, increasing the pressure in the bladder and decreasing the volume of urine the bladder can hold, which causes the individual to leak urine frequently and unexpectedly.<sup>5,6</sup> BOTOX® neurotoxin temporarily prevents muscle contractions by blocking the transmission of nerve impulses to the muscle, in this case, the bladder muscle, by selectively preventing the release of the neurotransmitter acetylcholine (ACh) at the neuromuscular junction.<sup>7</sup>

"Urinary incontinence or leakage is often considered a taboo subject. Studies have shown that many patients are undiagnosed and undertreated because they are too embarrassed to talk to their doctor about their symptoms. This is particularly true for patients with neurological conditions that are associated with urinary incontinence due to detrusor overactivity. Many of these patients don't get referred to a urologist who can diagnose and manage their bladder condition,"<sup>8</sup> said Dr. Victor Nitti\*, Vice-Chairman, Department of Urology, NYU Langone Medical Center, who was involved in the BOTOX® Phase III clinical trial program. "When not adequately managed, urinary incontinence due to detrusor overactivity in patients living with MS or SCI can lead to skin irritation, ulcers, pressure increases in the bladder that can cause kidney failure, as well as recurrent urinary tract infections."<sup>9</sup>

## **The BOTOX® Phase III Clinical Trial Program in MS and SCI Patients with Urinary Incontinence Due to Detrusor Overactivity**

Allergan's Phase III clinical trial program evaluated the safety and efficacy of BOTOX® injections as a treatment for adults with urinary incontinence due to detrusor overactivity associated with a neurologic condition such as MS or SCI. The program consisted of two pivotal Phase III trials, involving 691 patients (n=381 Multiple Sclerosis, 310 Spinal Cord Injury; T1 injury or below), who had an inadequate response to or were intolerant of an anticholinergic medication. Eligible patients needed to either be performing or willing and able to learn how to perform clean intermittent catheterization (CIC), a method used to empty their bladder.

Patients were randomized to receive a physician-administered treatment of 200U BOTOX® neurotoxin or placebo injected across the bladder muscle using a rigid or flexible cystoscope, a specialized tube with an optical lens at the end that is used to see inside the bladder. A cystoscope is placed into the bladder via the urethra under local anesthesia if requested by the patient.<sup>5,11</sup>

Results from the two Phase III clinical trials showed significant reductions in the frequency of urinary incontinence episodes in patients treated with 200U of BOTOX® neurotoxin compared to placebo within two weeks (15.3 and 18 episodes/week vs. 10 and 7.9, respectively) and approximately 20 fewer urinary incontinence episodes at week six versus placebo (19.9 and 19.6 episodes/week vs. 10.6 and 10.8, respectively).

The results were similar between placebo- and BOTOX® treated patients in the Phase III clinical trials in patients that received 200U of BOTOX® neurotoxin irrespective of concomitant anticholinergic use. BOTOX® is approved as a 200U dose for patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. Patients should be considered for retreatment with BOTOX® when the clinical effect of the previous treatment wears off. In the Phase III clinical trials, this was up to 10 months (42-48 weeks for the 200U BOTOX® group vs. 13-18 weeks for the placebo group).

The most frequently reported adverse reactions within 12 weeks of receiving BOTOX® injections for detrusor overactivity associated with a neurologic condition include urinary tract infection (24%), urinary retention (17%), hematuria (4%), fatigue (4%), and insomnia (2%).

The following adverse event rates were reported following initial injection (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), fatigue (6%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), insomnia (3%), and muscle spasm (2%).

### **About BOTOX® (onabotulinumtoxinA)**

BOTOX® is a prescription-only medical product that contains tiny amounts of highly purified botulinum toxin protein refined from the bacterium, *Clostridium botulinum*. BOTOX® has a unique, protected molecular structure that stabilizes the core toxin in BOTOX® from degradation. When injected at FDA-approved and labeled doses into a specific muscle or gland, BOTOX® neurotoxin is expected to diffuse locally and produce a safe and effective result by producing a localized and temporary reduction in the overacting muscle or gland, usually lasting up to approximately three months depending on the individual patient.

BOTOX® was first approved by the FDA 21 years ago for the treatment of strabismus and blepharospasm, two eye muscle disorders, making it the first botulinum toxin type A product approved in the world. Since its first approval, BOTOX® has been recognized by regulatory authorities worldwide as an effective treatment for 21 different indications in approximately 80 countries, benefiting millions of patients worldwide. In the United States, BOTOX® neurotoxin is also approved to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults, symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough, as well as for the treatment of increased muscle stiffness in elbow, wrist, and finger muscles in adult patients with upper limb spasticity. Most recently, in 2010, BOTOX® was approved by the FDA for the prophylactic treatment of headaches in adults with Chronic Migraine, a distinct and severe neurological disorder characterized by patients who have a history of migraine and suffer from headaches on 15 or more days per month with headaches lasting four hours a day or longer.

In addition to its therapeutic uses, the same formulation of BOTOX® with dosing specific to moderate to severe glabellar lines was approved by the FDA in 2002 under the trade name BOTOX® Cosmetic (onabotulinumtoxinA). BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines (frown lines between the eyebrows) associated with corrugator and/or procerus muscle activity in adult patients up to 65 years of age.

In addition to 21 years of clinical experience, the safety and efficacy of BOTOX® have been well-established in approximately 50 randomized, placebo-controlled clinical trials and in approximately 11,000 patients treated with BOTOX® and BOTOX® Cosmetic in Allergan's clinical trials.<sup>9</sup> Worldwide, approximately 26 million vials of BOTOX® and BOTOX® Cosmetic have been distributed and approximately 29 million treatment sessions have been performed over the past 20 years (1989-2009).<sup>10</sup> With approximately 2,300 articles on BOTOX® and BOTOX® Cosmetic in scientific and medical journals,<sup>11</sup> BOTOX® neurotoxin is one of the most widely researched medicines in the world.

## Indications

### **BOTOX<sup>®</sup> (onabotulinumtoxinA) & BOTOX<sup>®</sup> Cosmetic (onabotulinumtoxinA) Important Information**

## Indications

BOTOX<sup>®</sup> is a prescription medicine that is injected into muscles and used:

- treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease who still have leakage or experience too many 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<sup>®</sup> 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<sup>®</sup> 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 people 18 to 65 years of age for a short period of time (temporary).

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

It is not known whether BOTOX<sup>®</sup> and BOTOX<sup>®</sup> Cosmetic are 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<sup>®</sup> 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<sup>®</sup> is not meant to replace your existing physical therapy or other rehabilitation that your doctor may have prescribed.

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

## IMPORTANT SAFETY INFORMATION

**BOTOX<sup>®</sup> and BOTOX<sup>®</sup> 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<sup>®</sup> or BOTOX<sup>®</sup> 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<sup>®</sup> has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, urinary incontinence in adults with overactive bladder due to neurologic disease, or when BOTOX<sup>®</sup> Cosmetic has been used at the recommended dose to treat frown lines.

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

**Do not take BOTOX<sup>®</sup> 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.

**The dose of BOTOX<sup>®</sup> and BOTOX<sup>®</sup> Cosmetic is not the same as, or comparable to, another botulinum toxin product.**

**Serious and/or immediate allergic reactions have been reported.** These 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<sup>®</sup> or BOTOX<sup>®</sup> 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<sup>®</sup> or BOTOX<sup>®</sup> Cosmetic.

**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<sup>®</sup> for upper limb spasticity or for detrusor overactivity associated with a neurologic condition.

**Cornea problems have been reported.** Cornea (surface of the eye) problems have been reported in some people receiving BOTOX<sup>®</sup> for their blepharospasm, especially in people with certain nerve disorders. BOTOX<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> for their strabismus. Tell your doctor if you notice any new visual problems while receiving BOTOX<sup>®</sup>.

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

**Human albumin and spread of viral diseases.** BOTOX<sup>®</sup> and BOTOX<sup>®</sup> Cosmetic contain albumin, a protein component of human blood. The potential risk of spreading viral diseases (eg, Creutzfeldt-Jakob disease [CJD]) via human serum albumin is extremely rare. No cases of viral diseases or CJD have ever been reported in association with human serum albumin.

**Tell your doctor about all your medical conditions, including if you 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; pain or burning with urination, frequent urination, 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<sup>®</sup> or BOTOX<sup>®</sup> Cosmetic can harm your unborn baby); are breastfeeding or plan to breastfeed (it is not known if BOTOX<sup>®</sup> or BOTOX<sup>®</sup> 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<sup>®</sup> or BOTOX<sup>®</sup> 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<sup>®</sup> or BOTOX<sup>®</sup> 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*<sup>®</sup>, *Dysport*<sup>®</sup>, or *Xeomin*<sup>®</sup> 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 anti-coagulants (blood thinners).

**Other side effects of BOTOX<sup>®</sup> and BOTOX<sup>®</sup> 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, urinary tract infection and/or inability to empty your bladder on your own (in people being treated for urinary incontinence).

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.

Please see BOTOX<sup>®</sup> full [Product Information](#) including Boxed Warning and [Medication Guide](#).

Please see BOTOX<sup>®</sup> Cosmetic full [Product Information](#) including Boxed Warning and [Medication Guide](#).

#### **Forward-Looking Statement**

This press release contains "forward-looking statements", including but not limited to the statements by Drs. Whitcup and Nitti and other statements regarding the treatment of urinary incontinence, BOTOX<sup>®</sup> and the DIGNITY Clinical Trial Program as well as research and development outcomes, efficacy, adverse reactions and market and product potential. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or unknown risks or uncertainties materialize, actual results could vary materially from Allergan's expectations and projections. Risks and uncertainties include, among other things, general industry and pharmaceutical market conditions; technological advances and patents attained by competitors; challenges inherent in the research and development and regulatory processes; challenges related to new product marketing, such as the unpredictability of market acceptance for new pharmaceutical products and/or the acceptance of new indications for such products; inconsistency of treatment results among patients; potential difficulties in manufacturing a new product; general economic conditions; and governmental laws and regulations affecting domestic and foreign operations. Additional information concerning these and other risk factors can be found in press releases issued by Allergan, as well as Allergan's public periodic filings with the U.S. Securities and Exchange Commission, including the discussion under the heading "Risk Factors" in Allergan's 2010 Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q.

#### **About Allergan, Inc.**

Allergan is a multi-specialty health care company established more than 60 years ago with a commitment to uncover the best of science and develop and deliver innovative and meaningful treatments to help people reach their life's potential. Today, we have approximately 10,000 highly dedicated and talented employees, global marketing and sales capabilities with a presence in more than 100 countries, a rich and ever-evolving portfolio of pharmaceuticals, biologics, medical devices and over-the-counter consumer products, and state-of-the-art resources in R&D, manufacturing and safety surveillance that help millions of patients see more clearly, move more freely and express themselves more fully. From our beginnings as an eye care company to our focus today on several medical specialties, including ophthalmology, neurosciences, medical aesthetics, medical dermatology, breast aesthetics, obesity intervention and urologics, Allergan is proud to celebrate 60 years of medical advances and proud to support the patients and physicians who rely on our products and the employees and communities in which we live and work.

**Source: Allergan, Inc.**



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<sup>1</sup> BOTOX® Prescribing Information

<sup>2</sup> Allergan data on file; Epidemiology

<sup>3</sup> Manack et al. (2011). Epidemiology and Healthcare Utilization of Neurogenic Bladder Patients in a US Claims Database. *Neurourol. Urodynam.* 30(3), 1-7.

<sup>4</sup> Ginsberg D, et al. (2011, May) *Phase 3 Efficacy and Safety Study of OnabotulinumtoxinA in Patients With Urinary Incontinence Due to Neurogenic Detrusor Overactivity*. Presented at 107th Annual Meeting of the American Urological Association, Washington, DC

<sup>5</sup> Hansen RB, Biering-Sorensen F, Kristensen JK. Urinary incontinence in spinal cord injured individuals 10–45 years after injury. *Spinal Cord* 2009;48(1):27–33.

<sup>6</sup> Cohen BA. Identification, causation, alleviation, and prevention of complications (ICAP). An approach to symptom and disability management in multiple sclerosis. *Neurology*. 2008;71(suppl 3):S14-S20.

<sup>7</sup> BOTOX® USPI

<sup>8</sup> Tubaro A. (2004) Defining overactive bladder: epidemiology and burden of disease. *Urology*. 64(6 Suppl 1):2-6

<sup>9</sup> Allergan data on file; Medical Affairs

<sup>10</sup> Allergan data on file; Global Regulatory Affairs

<sup>11</sup> Allergan data on file; Global Literature & Information Services

*\*Dr. Nitti receives research support for conducting these clinical trials at NYU Langone, and is a member of an advisory board for Allergan, Inc.*