The medical uses of BOTOX[®]

More than skin deep



The medical uses of BOTOX[®] (Botulinum Toxin Type A)

Table of contents

| Page 3 | What is BOTOX*? | | |
|---------|---|--|--|
| Page 5 | How BOTOX [®] neurotoxin treatment works | | |
| Page 7 | What to expect from your BOTOX [®] treatment | | |
| Page 9 | Frequently asked questions about BOTOX® treat | | |
| Page 11 | BOTOX® treatment and your insurance coverage | | |
| Page 13 | Cervical dystonia and BOTOX® treatment | | |
| Page 21 | BOTOX® success stories | | |
| Page 25 | Living with cervical dystonia—tips for patients | | |
| Page 27 | Blepharospasm and BOTOX [®] treatment | | |
| Page 29 | Strabismus and BOTOX® treatment | | |
| Page 31 | Finding a doctor who injects BOTOX [®] | | |
| Page 33 | Patient support groups | | |
| | | | |



What is BOTOX[®]?

You may have heard of BOTOX[®] Cosmetic. But as you will learn in this brochure, the BOTOX[®] story is more than skin deep.

BOTOX[®] (Botulinum Toxin Type A) is an effective therapy that has been used to treat patients for a variety of conditions for more than 18 years. One of the most researched medicines in the world, BOTOX[®] treatment is approved for medical use in more than 75 countries.

First identified in the 1890s, BOTOX[®] is a purified protein that comes from the bacterium *Clostridium botulinum*. In slightly more than 100 years, our knowledge of botulinum toxin type A has expanded from the identification of the bacterium *C. botulinum* to the commercialization of botulinum toxin type A, as BOTOX[®] therapy.

In 1989, BOTOX[®] neurotoxin was approved by the Food and Drug Administration (FDA) for the treatment of blepharospam (clenched eyelids) and strabismus (crossed or misaligned eyes). In 2000, the FDA approved BOTOX[®] for the treatment of uncontrollable muscle tightening



or turning in the neck, known as cervical dystonia. Another milestone in the history of BOTOX[®] was its approval in 2004 to treat severe underarm sweating unresponsive to topical agents. The same formulation used to treat frown lines between the eyes was approved in 2002 as BOTOX[®] Cosmetic.

BOTOX[®] is different from other treatment options available to physicians and is made *only* by Allergan—a global specialty pharmaceutical and medical device company offering innovative products in more than 100 countries. BOTOX[®] treatment is produced under strict quality control standards by Allergan and is to be administered to patients only by licensed doctors.

Every drug approved by the FDA has product safety information for doctors and for patients. The highlighted gold sections in this brochure contain information about BOTOX[®] treatment, as well as detailed information about the drug itself. If you have any questions or concerns about any of the information contained in these sections, please do not hesitate to ask your doctor.

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.

How BOTOX[®] neurotoxin treatment works

When you experience muscle spasms and the associated pain of cervical dystonia, it is because your nerve cells are sending signals directly to your muscles, which cause these effects. BOTOX® (Botulinum Toxin Type A) treatment works by blocking these signals, which prevents the release of a substance known as *acetylcholine*.¹ Too much acetylcholine causes your muscles to become overactive and tense up. With BOTOX[®], muscle spasms may stop or become greatly reduced, resulting in relief.¹ There is also evidence from a study of patients that shows BOTOX[®] treatment may significantly reduce pain even before it achieves a significant muscle relaxation effect.²

Please discuss with your doctor any questions you may have about your treatment.

BOTOX[®] is approved for the treatment of strabismus (crossed eyes) and blepharospasm (eyelid spasms) associated with dystonia (muscle tightening), 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.

BOTOX[®] works by stopping nerves from releasing acetylcholine, a substance that transmits signals from nerves to muscles.



The signals that can cause muscle contractions and pain reach muscles through the nerves.



BOTOX[®] neurotoxin works in the muscle where it is injected to block signals that tell the muscle to contract.



As a result, muscle spasms stop or are greatly reduced, resulting in relief, which may last up to 3 months.

What to expect from your BOTOX[®] treatment

Once you and your doctor have determined that BOTOX[®] (Botulinum Toxin Type A) is right for you, your treatment will consist of a number of injections into the muscles selected by your doctor. BOTOX[®] injections will be given right in your doctor's office. The amount of BOTOX[®] and the locations of the injections will depend on your individual needs. You may have mild and temporary pain, tenderness, and/or bruising at the injection sites.

Because BOTOX[®] neurotoxin is injected directly into your affected muscles, it is not expected to be present in your bloodstream after injection at the recommended dosage. You should be able to leave your doctor's office after a brief recovery period.

How long does it take to see results? Not long at all. You may begin seeing an improvement in your symptoms within a few days (a few weeks for some conditions) of BOTOX[®] treatment and you may not have to visit your doctor for another injection for up to 3 months.



BOTOX[®] injections are given right in your doctor's office.

You may begin seeing positive effects within a few days of BOTOX[®] treatment, and you may not have to visit the doctor for another injection for up to 3 months.

Please talk to your doctor about any prescription and over-the-counter medications you may be taking for other medical conditions.

Important Safety Information Who should not be treated with BOTOX®

BOTOX[®] 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.



Frequently asked questions about BOTOX® treatment

Does BOTOX[®] treatment hurt?

The needles used to administer BOTOX[®] (Botulinum Toxin Type A) treatment are very fine, so most people experience only mild discomfort. It is uncommon for pain relief to be required, although some doctors suggest the use of a topical anesthetic cream before treatment.

Is BOTOX[®] Cosmetic the same as BOTOX[®]?

Yes. BOTOX[®] Cosmetic and BOTOX[®] are the same formulation. BOTOX[®] neurotoxin is one of the most widely researched medicines in the world and has been used for more than 18 years to effectively treat a variety of medical conditions. The same formulation with dosing specific to glabellar lines (frown lines between the brows) was approved in 2002 as BOTOX[®] Cosmetic.

Is it safe to get repeated injections of BOTOX?*

BOTOX[®] treatment is FDA approved for repeat injections. Patients around the world receive repeated injections of BOTOX[®] neurotoxin to effectively treat a variety of medical conditions.

Are there other treatments that are as effective as BOTOX[®] treatment?

BOTOX[®] is different from other therapies available to your physician. It has a unique formulation and mechanism of action that effectively stop muscle contractions and relieves pain in CD patients.

Is it true that some patients do not always have the same response to repeated BOTOX[®] injections?

There are many factors that impact the results of BOTOX[®] treatment. A very small percentage of people develop immunity to BOTOX[®] Other factors that impact results include the accuracy of injections, dosing, and changes in patients' conditions over time.

How do I know that I am receiving BOTOX[®] treatment and not a substitute product?

BOTOX[®] is a registered trademark of Allergan, Inc. The BOTOX[®] product is packaged in a glass vial with a purple lid labeled as BOTOX[®] and has an Allergan hologram on the side. You may want to ask your injector to see the vial to confirm that this is the product he or she is using for your treatment.



BOTOX[®] treatment and your insurance coverage

BOTOX[®] Reimbursement Solutions

Many insurance plans, including Medicare and Medicaid, cover the cost of BOTOX[®] (Botulinum Toxin Type A) treatment for certain conditions. Allergan, the maker of BOTOX[®], has made a service available to you and your doctor to determine if your plan covers the cost of BOTOX® treatment. The program is called **BOTOX[®] Reimbursement Solutions**, and our representatives are specially trained to help resolve BOTOX[®] insurance issues, answer questions, and file claims.

For more information about BOTOX[®] Reimbursement Solutions, call 1-800-44-BOTOX, Option 4. The hours are Monday through Friday, 9 AM to 8 PM, EST.

Cervical Dystonia Fund

If you are an eligible cervical dystonia patient, you may qualify for assistance from the Cervical Dystonia Fund. This program helps patients who are insured but unable to afford the out-of-pocket costs associated with any FDA-approved treatment for cervical dystonia. To receive help from the Cervical Dystonia Fund, you must:

- Meet certain criteria established by the National Organization for Rare Disorders (NORD) such as insurance criteria, financial needs, and medical needs
- Be a resident of the United States or Puerto Rico

For more information, call 1-800-44-BOTOX, Option 6.

BOTOX PATIENT ASSISTANCE[®] Program

The BOTOX PATIENT ASSISTANCE[®] Program is dedicated to helping financially eligible patients. There are certain financial and other requirements that you must meet in order to qualify for the program. You may gualify if you do not have insurance or if your insurance is not sufficient to meet your medical needs.

To receive help from the BOTOX PATIENT ASSISTANCE[®] Program, you must:

- Be uninsured or underinsured
- Have income less than or equal to 300% of the Federal Poverty Level. This is a figure defined by the US Federal Poverty Guidelines and is adjusted based on the number of household members. For more information, please visit http://aspe.hhs.gov/poverty
- Have a diagnosis supported by clinical studies that validate the use of BOTOX[®]
- Be a resident of the United States or Puerto Rico

If you think you may be eligible for the BOTOX PATIENT ASSISTANCE[®] Program, visit our Web site at www.BOTOXPatientAssistance.com to get more information or to download an application. You may also call us at 1-800-44-BOTOX, Option 6, where you will receive step-by-step help with the application process.



Cervical dystonia and BOTOX[®] treatment

Cervical dystonia definitions and symptoms

Cervical dystonia is a condition that causes the muscles in your neck to tighten or spasm without your control.³ If you have cervical dystonia, your head may turn in an unusual way, or it may be forced into an abnormal posture. The symptoms can make it hard to do simple daily tasks, such as dressing yourself or driving a car. But cervical dystonia can be treated. Getting treatment may help you return to your regular activities.

The first step to feeling better is talking to your doctor about your symptoms. Common signs of cervical dystonia often vary from person to person and may include any combination of the following:

- Muscle spasms or tightness³
- Neck pain (reported in up to 91% of patients)⁴
- Aches and pains around the neck that worsen over time³
- Head turning, pulling, or shifting to one side³
- Shaking or tremor³
- Symptoms that improve after sleep or rest³
- Symptoms that worsen after stress or activity³
- Problems swallowing⁵

If you suspect that you have cervical dystonia, be sure to talk to your doctor.

"It all started with a pain in the base of my neck. Then my neck started to pull and shake when I tried to pull it back. It was tough. I was fighting it every day. I was at war with my neck."

Gus, cervical dystonia patient

Important Safety Information Warnings

Serious heart problems and serious allergic reactions have been reported rarely. If you think you're having an allergic reaction or other unusual symptoms such as difficulty swallowing, speaking or breathing, call your doctor immediately.



Cervical dystonia and BOTOX® treatment

Diagnosing cervical dystonia

Diagnosing cervical dystonia can be a challenge, especially in its early or mild stages.³ This is because the symptoms may be subtle, or slight at first, and differ from person to person. Cervical dystonia is sometimes diagnosed incorrectly because it resembles other physical complaints such as stiff neck or stress. In some cases, patients may suffer with cervical dystonia for a year or more before being diagnosed and treated.⁶

In testing for cervical dystonia, many different tests may be used including brain imagings, blood tests, electroencephalographies (EEGs), electromyographies (EMGs), and video monitoring, among others. When people see their doctors, the blood tests, magnetic resonance imagings (MRIs), and neurological examinations are usually normal.^{7,8} An evaluation may also include genetic testing in some situations.³ These tests may be used to rule out other conditions, leaving cervical dystonia as the diagnosis.

To provide additional information that can help doctors diagnose cervical dystonia, movement disorder experts have developed these simple screening questions⁹:

- Do you find your head involuntarily turning, tilting, or shifting in any direction, with or without pain?
- Does your head involuntarily shake or jerk, with or without pain?

Cervical dystonia is a progressive disease

Cervical dystonia is a progressive disease, meaning that the symptoms may get worse with time. In approximately 20% of people, cervical dystonia symptoms go away completely. This is known as remission. However, it is important to understand that the symptoms often return.³ For most people with cervical dystonia, their symptoms usually stop worsening after 5 years.⁶

Generally, if you begin to experience cervical dystonia while young, it may spread to other parts of your body, whereas, if you begin to experience symptoms as an adult, it may only involve the neck muscles.¹⁰

There are many causes of cervical dystonia; through an accident, through inherited genes, or through some unknown cause. If you are interested in more information, please talk to your doctor.

Important Safety Information Warnings

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[®].

Cervical dystonia and BOTOX® treatment

How cervical dystonia impacts daily activities

If you have cervical dystonia, you may find it hard to do simple things. Dressing, shaving, housework, driving a car, or using a computer can become a challenge. Also, cervical dystonia often affects people who have spent years in jobs or hobbies that require repetitive movements such as musicians, writers, artists, golfers, rowers, and tennis players.¹⁰

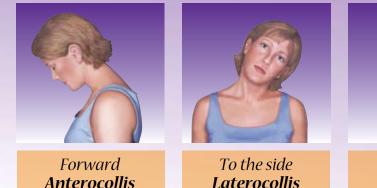
Although there is no cure for cervical dystonia, there is a good chance that your symptoms can be successfully managed with proper treatment. It may help to know that there are healthcare professionals who understand your condition and are experienced in helping patients find relief.

As medical knowledge about cervical dystonia continues to grow, and with wider availability of helpful medicines, there is more reason than ever to be hopeful about treatment.

Types of cervical dystonia

Cervical dystonia causes constant muscle tension—that's the dystonia part—and it occurs mainly in the neck area, in what is called the cervical spine. Tense muscles in the neck pull the head in abnormal movements and postures

There are 4 main types of cervical dystonia, defined by which way the head is tilting:



B Ro

Sometimes the head is pulled in 2 or more directions at the same time, such as forward and to the side.¹¹ Most patients (up to 80%) have a combination of these postures.¹² Cervical dystonia may also be called *spasmodic*, if there are sudden, involuntary muscle contractions, or *sustained*, if the muscle tension is continuous.¹¹

Important Safety Information Warnings

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.



Backward **Retrocollis**

Rotated **Torticollis**

Cervical dystonia and BOTOX® treatment

Treatments for cervical dystonia

Doctors have a number of options for treating cervical dystonia. The most commonly chosen treatment is BOTOX[®] (Botulinum Toxin Type A) neurotoxin. BOTOX[®] is considered a first-line therapy for cervical dystonia,¹³ which means that doctors may choose to go straight to BOTOX[®] neurotoxin, without trying other options. Your physician determines exactly which muscles are troubling you and injects BOTOX[®] neurotoxin into them.

BOTOX[®] is often used in combination with physical therapy.¹⁴ Oral prescription drugs may also be used. These include primarily muscle relaxants, antiseizure medications, and anticholinergics—a type of drug that blocks impulses from the nervous system.¹¹ Surgery on the involved nerves may also be an option, but surgery is rarely used, now that BOTOX[®] neurotoxin is available.¹¹

With BOTOX[®] treatment, many cervical dystonia patients get relief from their overly active or tense neck muscles. BOTOX[®] may also decrease their pain associated with cervical dystonia even before it relaxes their neck muscles.

How BOTOX[®] can help

For the vast majority of people with cervical dystonia, BOTOX[®] injections are very effective. BOTOX[®] therapy stops or greatly reduces neck pain and muscle spasms. Results from a key clinical study showed that after receiving BOTOX[®] neurotoxin injections, patients with cervical dystonia had

improved head posture, pain that was less intense and occurred less often, and an improved ability to function in certain daily activities.¹⁵ Another study showed that pain relief may happen even before muscles become significantly relaxed.²

These are all important benefits for people with cervical dystonia. For many of them, BOTOX[®] injections can be an effective cervical dystonia treatment. After a BOTOX[®] neurotoxin treatment, many cervical dystonia patients experience up to 3 months of relief from muscle spasms. That is how long it takes the nerves to resume the release of acetylcholine.

Here's what BOTOX[®] neurotoxin can do for you:

Stop or greatly reduce neck pain and muscle spasms
Improve head posture
Reduce intensity and frequency of neck pain
Improve your ability to perform certain daily activities

BOTOX[®] success story



Kathleen, age: 34

Treatments preceding cervical dystonia diagnosis:

- Massage
- Acupuncture
- Traction
- Steroids
- Psychotropics
- Chiropractic adjustment

Duration of time from initial symptoms to diagnosis: 17 years

Presenting symptoms:

- Neck pain
- Tremor
- Stiffness
- Limited range of motion

Treatment regimen:

BOTOX[®] (Botulinum Toxin Type A) injections "Occasionally, my neck might grab for a second...and then it just releases. It just doesn't have that power anymore, to hold onto me. So no more neck pain."

BOTOX® success story



Gus, age: 32

Treatments preceding cervical dystonia diagnosis:

- Analgesics
- Anti-inflammatories
- Physical therapy

Duration of time from initial symptoms to diagnosis: 1 year

Presenting symptoms:

- Neck pain
- Tremor
- Right torticollis

Treatment regimen:

BOTOX[®] (Botulinum Toxin Type A) injections and physical therapy "My outlook is to continue my treatments as long as they're needed and stay positive, live life, just live as much of a normal life as I can."

Ask your doctor if BOTOX[®] treatment is right for you

Important Safety Information Precautions

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

Living with cervical dystonia –tips for patients

In addition to taking your medications and following your doctor's advice, there is more you can do to relieve your cervical dystonia symptoms:

- Avoid stress and stressful situations, whether they occur in the workplace, in public places, or at home
 - It is important to understand that stress can exacerbate the symptoms of cervical dystonia¹⁴
- Stay well rested (which can improve the symptoms of cervical dystonia) and avoid overexertion
- Eat sensibly and nutritionally
 - Avoid those foods that stimulate the nerves. Caffeine, sugar, and chocolate can sometimes activate cervical dystonia symptoms¹⁶
- Consult with your doctor regarding an exercise program
 - Light yoga, simple calisthenics, water exercises, and deep breathing exercises can help relax both mind and body¹⁶
- Connect with support groups in your area for additional resources and education (some are listed at the back of this brochure)

Here is a sensory exercise you may want to try...

Cervical dystonia is the most common focal dystonia that responds to *sensory tricks*. For example, patients with cervical dystonia may place their hand on the side of their face. chin, or back of the head. This may help reduce the intensity of the symptoms. Lightly touching or applying pressure to certain areas of the head—on the side that is opposite to that which the head is turned—may temporarily allow correction of abnormal head position.¹⁴

If your doctor decides you should be treated for cervical dystonia, be sure to keep track of any improvements or worsening of your symptoms as well as how you react to treatment. Share all your observations with your doctor—be an active partner in managing your cervical dystonia.

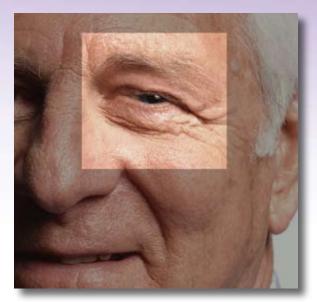
Important Sa Side effects Localized pai be associated In cervical dy effects follow swallowing ((12%), neck

Important Safety Information

Localized pain, tenderness, 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%).

Blepharospasm and BOTOX® treatment



Blepharospasm definitions and symptoms

Blepharospasm is a muscle disorder characterized by involuntary spasm of the muscles around the eye, resulting in uncontrolled narrowing or closing of the eyelid.¹⁷ The gravest consequence of blepharospasm is impairment of vision. Approximately 56% of people with blepharospasm are female, and the average age of onset is 56 years.^{17,18}

Diagnosing blepharospasm

Doctors diagnose blepharospasm based on key signs and symptoms. In the early stages of blepharospasm, patients may complain of irritation and discomfort of the eyelids as well as increased blinking.¹⁷

As blepharospasm progresses, blinking usually becomes more frequent, forceful, and uncontrollable. Bright light, noise, stress, polluted air, or wind can make the symptoms worse.¹⁹ Without proper medical treatment, few blepharospasm patients get better on their own.¹⁷

How BOTOX[®] treatment can help

BOTOX[®] (Botulinum Toxin Type A) neurotoxin has been the principal treatment for blepharospasm since FDA approval in 1989. When injected directly in the affected muscles around the eyes, the neurotoxin relieves the muscle spasm and the forceful involuntary closing of the eyelid. BOTOX[®] treatment can be repeated approximately every 3 months as long as the patient continues to respond and does not have an allergic reaction.¹³

BOTOX[®] is approved for the treatment of strabismus (crossed eyes) and blepharospasm (eyelid spasms) associated with dystonia (muscle tightening), 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 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.



Strabismus and BOTOX[®] treatment



Strabismus definitions and symptoms

Strabismus is the name doctors give a group of disorders in which muscles tighten around the eye, resulting in pulling of the eyeball to the side. Strabismus is also known as *crossed eyes*. A common form is *esotropia*, or convergent strabismus, which is when one or both eyes turn toward the nose.²⁰ Other symptoms include squinting, tilting the head to look at things, frequent eye movements, headache, rubbing the eyes, tearing, and double vision.

Today, strabismus is typically treated early in childhood (before 4 to 6 years of age) by orthoptic training (eye exercises) and/or corrective lenses. In some cases where strengthening techniques are not successful, surgery may be required to realign the eye muscles.²⁰

In adults, strabismus can occur gradually or rapidly. When it happens gradually, strabismus is usually the result of loss of muscle tone. When it happens rapidly, strabismus may be a result of an injury or a serious illness.²⁰

Diagnosing strabismus

When it occurs in children, strabismus is usually noticed first by parents or a doctor because the child's eyes appear to be positioned abnormally. An eye examination confirms the diagnosis and identifies the type of strabismus.

Strabismus should never be ignored on the assumption that a child will outgrow it. Unless treated before age 9, strabismus can lead to permanent loss of sight in the deviating eye.²⁰

How BOTOX[®] treatment can help

In treating strabismus, only BOTOX[®] (Botulinum Toxin Type A) treatment is believed to have an effect on pairs of muscles. Upon being injected with BOTOX[®] neurotoxin, the muscles weaken and become slightly relaxed. This allows the muscles on the other side of the eye to contract.^{13,21}

Through this double action, BOTOX[®] treatment is thought to help the eyes align, or look in the same direction.

Important Safety Information Side effects

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%).

Finding a doctor who injects BOTOX[®]

If you would like to discuss your condition with a doctor who injects BOTOX® (Botulinum Toxin Type A), you can find one by visiting www.BOTOXMedical.com and using our Physician Locator.

To locate a doctor who injects BOTOX[®] neurotoxin, simply visit these Web sites: The official BOTOX[®] Web site:

www.BOTOXMedical.com

WebMD[®] Physician Directory:

http://doctor.webmd.com/physician_finder

AMA DoctorFinder:

http://webapps.ama-assn.org/doctorfinder/home.html

For more information about BOTOX^{*}, please visit our Web site at

www.BOTOXMedical.com

or call

1-800-44-BOTOX





Patient support groups

Your healthcare provider is the best source of information for your condition and its treatment. In addition, there are many organizations that offer support, education, and services for patients. Some of them may even have local chapters in your area.

Benign Essential Blepharospasm Research Foundation (BEBRF) 1-409-832-0788 www.blepharospasm.org

Care4Dystonia, Inc. www.care4dystonia.org

Dystonia Medical Research Foundation (DMRF) 1-312-755-0198 1-800-377-DYST (1-800-377-3978) www.dystonia-foundation.org

The National Spasmodic Torticollis Association (NSTA) 1-714-378-9837 1-800-487-8385 www.torticollis.org

ST/Dystonia, Inc. 1-262-560-9534 1-888-445-4588 www.spasmodictorticollis.org

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Full prescribing information has been provided to your doctor.

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BOTOX[®] (Botulinum Toxin Type A)

Purified Neurotoxin Complex

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612

DESCRIPTION

BOTOX® (Botulinum Toxin Type A) Purified Neurotoxin Complex is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain Clostridium botulinum type A grown in a medium containing casein hydrolysate, glucose and yeast extract. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drving.

Re-order: APC102212006

One Unit of BOTOX® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX®. Due to specific details of this assay such as the vehicle dilution scheme and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of $\textbf{BOTOX}^{\textcircled{0}}$ cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of BOTOX® is approximately 20 units/nanogram of neurotoxin protein complex.

Each vial of BOTOX® contains 100 Units (U) of Clostridium botulinum type A neurotoxin complex, 0.5 milligrams of Albumin Human, and 0.9 milligrams of sodium chloride in a sterile, vacuum-dried form without a preservative.

CLINICAL PHARMACOLOGY:

BOTOX® blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX® produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX®.

When injected intradermally, BOTOX® produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Pharmacokinetics

Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.

Clinical Studies:

Cervical Dystonia:

A phase 3 randomized, multi-center, double blind, placebo-controlled study of the treatment of cervical dystonia was conducted.¹ This study enrolled adult patients with cervical dystonia and a history of having received BOTOX® in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of BOTOX®. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX® group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physicians Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from -4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 1

Table 1: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

| | Placebo N=82 | BOTOX [®] N=88 | 95% CI on Difference |
|---|-----------------|----------------------------|-----------------------------|
| Baseline CDSS | 9.3 | 9.2 | |
| Change in CDSS at Week 6 | -0.3 | -1.3 | (-2.3, 0.3) [a,b] |
| Percentage Patients with Any Improvement on Physicians Global Assessment | 31% | 51% | (5%, 34%) [a] |
| Pain Intensity Baseline | 1.8 | 1.8 | |
| Change in Pain Intensity at Week 6 | -0.1 | -0.4 | (-0.7, -0.2) ^[C] |
| Pain Frequency Baseline | 1.9 | 1.8 | |
| Change in Pain Frequency at Week 6 | -0.0 | -0.3 | (-0.5, -0.0) [C] |

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.

[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests

[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65 (see also PRECAUTIONS: Geriatrics). There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

There were several randomized studies conducted prior to the phase 3 study which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of BOTOX®

In the phase 3 study the median total **BOTOX[®]** dose in patients randomized to receive **BOTOX[®]** (n=88) was 236 Units. with 25th to 75th percentile ranges of 198 to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles: 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 2 The total dose and muscles selected were tailored to meet individual patient needs

Table 2: Number of Patients Treated Per Muscle and Fraction of Total Dose Injected into Involved Muscles

| Muscle* | Number of Patients Treated in this Muscle (N=88) | Mean % Dose per Muscle | Mid-Range of % Dose per Muscle |
|---------------------------|--|---------------------------|--------------------------------------|
| Splenius capitis/cervicis | 83 | 38 | 25-50 |
| Sternocleidomastoid | 77 | 25 | 17-31 |
| Levator scapulae | 52 | 20 | 16-25 |
| Trapezius | 49 | 29 | 18-33 |
| Semispinalis | 16 | 21 | 13-25 |
| Scalene | 15 | 15 | 6-21 |
| Longissimus | 8 | 29 | 17-41 |

*The mid-range of dose is calculated as the 25th to 75th percentiles NOTE: There were 16 patients who had additional muscles injected.

Primary Axillary Hyperhidrosis:

The efficacy and safety of BOTOX® for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies

Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1= "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities." A total of 322 patients were randomized in a 1.1.1 ratio to treatment in both axillae with either 50 Units of BOTOX®, 75 Units of BOTOX®, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX® groups than in the placebo group (p < 0.001), but was not significantly different between the 2 BOTOX[®] doses (See Table 3)

Table 3: Study 1 - Study Outcomes

| Treatment Response | BOTOX® 50 Units N = 104 | BOTOX [®] 75 Units N=110 | Placebo N= 108 | BOTOX [®] 50-placebo (95% CI) | BOTOX [®] 75-placebo (95% Cl) |
|---|-------------------------------|---|-------------------|--|--|
| HDSS Score change ≥2 % (n) ^a | 55% (57) | 49% (54) | 6% (6) | 49.3% (38.8, 59.7) | 43% (33.2, 53.8) |
| >50% decrease in axillary sweat production %(n) | 81% (84) | 86% (94) | 41% (44) | 40% (28.1, 52.0) | 45% (33.3, 56.1) |

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in BOTOX®-treated patients with either dose was 201 days. Among those who received a second **BOTOX[®]** injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive and any alterations to the anatomy due to prior surgical procedures. An understanding of standard either 50 Units of BOTOX® (n=242) or placebo (n=78). Treatment responders were defined electromyographic techniques is also required for treatment of strabismus and may be useful for as subjects showing at least a 50% reduction from baseline in axillary sweating measured by the treatment of cervical dystonia. gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders Caution should be used when BOTOX® treatment is used in the presence of inflammation at were 91% (219/242) in the BOTOX® group and 36% (28/78) in the placebo group, p < 0.001. the proposed injection site(s) or when excessive weakness or atrophy is present in the target The difference in percentage of responders between BOTOX® and placebo was 55% (95% muscle(s). CI = 43.3, 65.9).

Blepharospasm

Patients with smaller neck muscle mass and patients who require bilateral injections into the Botulinum toxin has been investigated for use in patients with blepharospasm in several sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the studies. In an open label uncontrolled study, 27 patients with essential blepharospasm dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. were injected with 2.0 Units of BOTOX® at each of six sites on each side. One patient Injections into the levator scapulae may be associated with an increased risk of upper respiratory had not received any prior treatment. Twenty-six of the patients had not responded to infection and dysphagia therapy with benztropine mesulate, clonazepam and/or baclofen. Three of the 26 patients continued to experience spasms following muscle stripping surgery. Twenty-five of the 27 Primary Axillary Hyperhidrosis: patients treated with botulinum toxin reported improvement within 48 hours. One patient was Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g. hyperthyroidism) controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebocontrolled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12.5 weeks prior to the need for re-treatment.4

Strabismus:

It is postulated that when used for the treatment of strabismus, the administration of **BOTOX®** effects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the muscle's antagonist; it was on the basis of this hypothesis that clinical studies were conducted. Six hundred seventy-seven patients with strabismus treated with one or more injections of **BOTOX®** were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.⁵ These results are consistent with results from additional open label trials which were conducted for this indication.4

INDICATIONS AND USAGE:

BOTOX® is indicated 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 indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately Patients or caregivers should be advised to seek immediate medical attention if swallowing, speech managed with topical agents. or respiratory disorders arise

BOTOX® is indicated 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.

CONTRAINDICATIONS

BOTOX[®] is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS

The recommended dosage and frequency of administration for BOTOX® should not be exceeded. Risks resulting from administration at higher dosages are not known.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined. If such a reaction occurs further injection of BOTOX® should be discontinued and appropriate medical therapy immediately institued.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should only receive BOTOX® with caution. Patients with neuromuscular disorders and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal may be at increased risk of clinically significant systemic effects including severe dysphagia malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very and respiratory compromise from typical doses of BOTOX®. Published medical literature has sensitive species to BOTOX® reported rare cases of administration of a botulinum toxin to patients with known or unrecognized There are no adequate and well-controlled studies of BOTOX® in pregnant women. Because neuromuscular disorders where the patients have shown extreme sensitivity to the systemic animal reproductive studies are not always predictive of human response, BOTOX® should be effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. administered during pregnancy only if the potential benefit justifies the potential risk to the fetus. If

Dvsphagia

Dysphagia 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. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

Human Albumin

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS:

The safe and effective use of BOTOX® depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX® must understand the relevant neuromuscular and/or orbital anatomy of the area involved

Cervical Dystonia

- to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.
- The safety and effectiveness of BOTOX® for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively.

Blepharospasm.

Reduced blinking from BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. One case of corneal perforation in an aphakic eve requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Strahismus:

During the administration of **BOTOX[®]** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms.

Information for Patients:

- Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia, which is typically mild to moderate, but could be severe. Rare consequences of severe dysphagia include aspiration, dyspnea, pneumonia, and the need to reestablish an airway.
- As with any treatment with the potential to allow previously sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually following the administration of **BOTOX®**.

Drug Interactions:

Co-administration of **BOTOX®** and aminoglycosides⁶ or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Pregnancy: Pregnancy Category C

When pregnant mice and rats were injected intramuscularly during the period of organogenesis. the developmental NOEL of BOTOX® was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification which may be reversible.

- this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations which have been observed in rabbits.
- Carcinogenesis, Mutagenesis, Impairment of fertility: Long term studies in animals have not been performed to evaluate carcinogenic potential of BOTOX®
- The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 U/kg was 4 U/kg in male rats and 8 U/kg in female rats. Higher doses were associated with dose-dependent reductions in fertility in male rats (where limb weakness resulted in the inability to mate), and an altered estrous cycle in female rats. There were no adverse effects on the viability of the embryos
- Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX® is administered to a nursing woman.
- Pediatric use: Safety and effectiveness in children below the age of 12 have not been established for blepharospasm or strabismus, or below the age of 16 for cervical dystonia or 18 for hyperhidrosis.

Geriatric use: Clinical studies of **BOTOX**[®] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, does selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

General:

There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin.

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events have been reported since the drug has been marketed and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

In general, adverse events occur within the first week following injection of **BOTOX®** and while generally transient may have a duration of several months. Localized pain, tenderness, and/or bruising may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin.

Cervical Dystonia:

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of **BOTOX**[®], the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).⁷

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported rarely.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of **BOTOX[®]** resulting from the spread of the toxin outside the injected muscles.

The most common severe adverse event associated with the use of **BOTOX[®]** injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea. (See **Warnings**). Most dysphagia is reported as mild or moderate in severity. However, it may rarely be associated with more severe signs and symptoms (See **Warnings**).

Additionally reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of **BOTOX**[®] for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

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Primary Axillary Hyperhidrosis: The most frequently reported adverse events (3-

10% of patients) following injection of BOTOX[®]
 in double-blind studies included injection site
 pain and hemorrhage, non-axillary sweating,
 infection, pharyngitis, flu syndrome, headache,
 fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to $\textbf{BOTOX}^{\textcircled{M}}$ 50 Units and 110 patients exposed to $\textbf{BOTOX}^{\textcircled{M}}$ 75 Units in each axilla.

Because clinical trials are conducted under widely

varying conditions, adverse events observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not be predictive of rates observed in practice.

Blepharospasm:

In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured **BOTOX**[®], the most frequently reported treatment-related adverse reactions were ptosis (20.8%), superficial punctate keratitis (6.3%) and eye dryness (6.3%).⁸

In this study, the rate for ptosis in the current **BOTOX**[®] treated group (20.8% of patients) was significantly higher than the original **BOTOX**[®] treated group (4.0% of patients) (p=0.014%). All of these events were mild or moderate except for one case of ptosis which was rated severe.

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia and entropion, diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder (one case of an aphakic eye), reduced blinking from **BOTOX**[®] injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and corneal ulceration. Perforation occurred in the aphakic eye and required corneal grafting.

A report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus:

Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviation, especially with higher doses of **BOTOX®**. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus are 15.7% and 16.9%, respectively.⁴

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision, or past-pointing. Covering the affected eye may alleviate these symptoms.

The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection.

Ptosis (0.3%) and vertical deviation greater than two prism diopters (2.1%) were reported to persist for over six months in a larger series of 5587 injections of horizontal muscles in 3104 patients.

In these patients, the injection procedure itself caused nine scleral perforations. A vitreous hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar hemorrhages occurred without visual loss. Decompression of the orbit after five minutes was done to restore retinal circulation in one case. Five eyes had pupillary change consistent with ciliary ganglion damage (Adie's pupil).

One patient developed anterior segment ischemia after receiving **BOTOX**[®] injection into the medial rectus muscle under direct visualization for esotropia.

Immunogenicity:

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX**[®] treatment by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX**[®] has not been well studied.

In the phase 3 cervical dystonia study¹ that enrolled only patients with a history of receiving **BOTOX**[®] for multiple treatment sessions, at study entry there were 192 patients with antibody assay results, of whom 33 (17%) had a positive assay for neutralizing activity. There were 96 patients in the randomized period of the phase 3 study with valid assays at both study entry and end and who were neutralizing activity negative at entry. Of these 96, 2 patients (2%) converted to positive for neutralizing activity. Both of these converting patients were among the 52 who had received two **BOTOX**[®] treatments between the two assays; none were in the group randomized to placebo in the controlled comparison period of the study.

In the randomized period of the cervical dystonia study, patients in the **BOTOX**[®] group whose baseline assays were neutralizing antibody negative showed improvements on CDSS (n=64, mean CDSS change -2.1) while patients whose baseline assays were neutralizing antibody positive did not (n=14, mean CDSS change +1.1). However, in uncontrolled studies there are also individual patients who are perceived as continuing to respond to treatments despite the presence of neutralizing activity. Not all patients who become non-responsive to **BOTOX**[®] after an initial period of clinical response have demonstrable levels of neutralizing activity.

One patient among the 445 hyperidrosis patients with analyzed specimens showed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to $BOTOX^{\textcircled{O}}$ in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, concomitant medications and underlying disease. For these reasons, comparison of the incidence of neutralizing activity to **BOTOX**[®] with the incidence reported to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that $BOTOX^{\textcircled{O}}$ injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

OVERDOSAGE:

Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis.

An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. In the event of an overdose or injection into the wrong muscle, immediately contact Allergan for additional information at (800) 433-8871 from 7:00 AM to 3:00 PM Pacific Standard Time, or at (714) 246-5954 for a recorded message at other times. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

DOSAGE AND ADMINISTRATION:

 $BOTOX^{(0)}$ is supplied in a single use vial. Because the product and diluent do not contain a preservative, once opened and reconstituted, store in a refrigerator and use within four hours. Discard any remaining solution. Do not freeze reconstituted $BOTOX^{(0)}$.

BOTOX® is to be reconstituted with sterile, non-preserved saline prior to intramuscular injection.

General:

An injection of **BOTOX[®]** is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin (see Dilution Table) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile, needle and syringe should be used to enter the vial on each occasion for removal of **BOTOX[®]**.

The method utilized for performing the potency assay is specific to Allergan's Botulinum Toxin Type A. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various potency assays. Units of biological activity of Botulinum Toxin Type A cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal dose-activity relationships to human dose relationships.

Cervical Dystonia:

The phase 3 study enrolled patients who had extended histories of receiving and tolerating **BOTOX**[®] injections, with prior individualized adjustment of dose. The mean **BOTOX**[®] dose administered to patients in the phase 3 study was 236 Units (25th to 75th percentile range 198 Units to 300 Units). The **BOTOX**[®] dose was divided among the affected muscles (see Clinical Studies: Cervical Dystonia).

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response and adverse event history.

The initial dose for a patient without prior use of **BOTOX[®]** should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscles to 100 Units or less may decrease the occurrence of dysphagia (see **PRECAUTIONS: Cervical Dystonia**).

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the phase 3 study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

Primary Axillary Hyperhidrosis:

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's lodine-Starch Test. **BOTOX®** is reconstituted with 0.9% non-preserved sterile saline (100 Units/4 mL). Using a 30 gauge needle, 50 Units of **BOTOX®** (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine Starch Test Procedure:

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 1:

Figure 1:



Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink do not inject **BOTOX®** directly through the ink mark to avoid a permanent tattoo effect.

Blepharospasm:

For blepharospasm, reconstituted **BOTOX**[®] (see Dilution Table) is injected using a sterile, 27 - 30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 - 2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pretarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient-usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5.0 Units per site. Some tolerance may be found when **BOTOX**[®] is used in treating blepharospasm if treatments are given any more frequently than every three months, but it is rare to have the effect be permanent.

The cumulative dose of **BOTOX®** treatment in a 30-day period should not exceed 200 Units.

Strabismus:

BOTOX[®] is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for **BOTOX[®]** injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

Note: The volume of $BOTOX^{\textcircled{0}}$ injected for treatment of strabismus should be between 0.05 - 0.15 mL per muscle.

The initial listed doses of the reconstituted **BOTOX**[®] (see Dilution Table below) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

- I. Initial doses in Units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.
- A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 - 2.5 Units in any one muscle.
- B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 5.0 Units in any one muscle.
- C. For persistent VI nerve palsy of one month or longer duration: 1.25 2.5 Units in the medial rectus muscle.
- II. Subsequent doses for residual or recurrent strabismus.
- A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- B. Patients experiencing adequate paralysis of the target muscle that require subsequent

injections should receive a dose comparable to the initial dose.

- C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- E. The maximum recommended dose as a single injection for any one muscle is 25 Units.

Dilution Technique:

Prior to injection, reconstitute vacuum-dried **BOTOX**[®], with sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe, and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX**[®] with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX**[®] should be administered within four hours after reconstitution.

During this time period, reconstituted **BOTOX**[®] should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX**[®] should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

Dilution Table

| Diluent Added (0.9% Sodium Chloride Injection) | Resulting dose Units per 0.1 mL |
|---|------------------------------------|
| 1.0 mL | 10.0 Units |
| 2.0 mL | 5.0 Units |
| 4.0 mL | 2.5 Units |
| 8.0 mL | 1.25 Units |

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the **BOTOX[®]** dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose.)

HOW SUPPLIED:

BOTOX[®] is supplied in a single use vial. Each vial contains 100 Units of vacuum-dried Clostridium botulinum type A neurotoxin complex. NDC 0023-1145-01.

Vials of **BOTOX®** have a holographic film on the vial label that contains the name "Allergan" within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note the holographic film on the label is absent in the date/batch area.) If you do not see the lines of rainbow color or the name "Allergan," do not use the product and contact Allergan for additional information at (800) 890-4345 from 7:00 AM to 3:00 PM Pacific Standard Time.

Rx Only

Single use vial.

Storage:

Unopened vials of **BOTOX[®]** should be stored in a refrigerator (2° to 8° C) for up to 36 months. Do not use after the expiration date on the vial. Administer **BOTOX[®]** within 4 hours of reconstitution; during this period reconstituted **BOTOX[®]** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX[®]** should be clear, colorless and free of particulate matter.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

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Revised October 2006

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc., 2525 Dupont Dr., Irvine, CA 92612

US Patents 6,974,578; 6,683,049; 6,896,886

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