Indications

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

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

IMPORTANT SAFETY INFORMATION

BOTOX® and BOTOX® Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX® or BOTOX® 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

Please see additional Indications and Important Safety Information about BOTOX® inside.

BOTOX®
onabotulinumtoxinA

The medical uses of BOTOX® (onabotulinumtoxinA)

Indications (continued)

BOTOX® is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough in people 18 years and older.

It is not known whether BOTOX® is safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

BOTOX® Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in people 18 to 65 years of age for a short period of time (temporary).

Table of contents

What is BOTOX®?

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

BOTOX® (onabotulinumtoxinA) is an effective therapy that has been used to treat patients for approximately 20 years. One of the most researched medicines in the world, BOTOX® treatment is approved for medical use in approximately 75 countries.

First identified in the 1890s, BOTOX® is a purified protein that comes from the bacterium *Clostridium botulinum*. In approximately 100 years, our knowledge of Botulinum Toxin Type A has expanded from the identification of the bacterium *C. botulinum* to the commercialization of BOTOX® as the first approved botulinum toxin therapy in the United States.

In 1989, BOTOX® neurotoxin was approved by the Food and Drug Administration (FDA) for the treatment of blepharospasm (eyelid spasms) 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 symptoms of severe underarm sweating when topical medicines don't work well enough. The same formulation with dosing specific to temporarily treat moderate to severe frown lines between the brows for people ages 18 to 65 was approved in 2002 as BOTOX® Cosmetic.

BOTOX® (onabotulinumtoxinA) is made *only* by Allergan—a global specialty pharmaceutical and medical device company offering innovative products in approximately 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 blue 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.

IMPORTANT SAFETY INFORMATION (continued)

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® or BOTOX® Cosmetic:

- **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

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

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How BOTOX® neurotoxin treatment works

When you experience muscle spasms, it is because your nerve cells are sending signals directly to your muscles, which causes this effect. BOTOX® (onabotulinumtoxinA) 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® neurotoxin, muscle spasms may stop or become greatly reduced,[1] resulting in relief.

You may also experience neck pain associated with cervical dystonia. BOTOX® is believed to work in a similar way to block the nerve signals that cause neck pain, resulting in relief. There is evidence from a study of patients that shows BOTOX® treatment may significantly reduce neck pain even before muscle spasms are reduced.[2] The exact way BOTOX® works to reduce neck pain in cervical dystonia is not known.

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

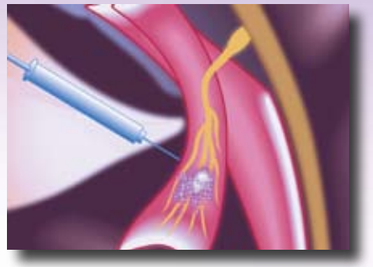
IMPORTANT SAFETY INFORMATION (continued)

The dose of BOTOX® is not the same as, or comparable to, another botulinum toxin product.

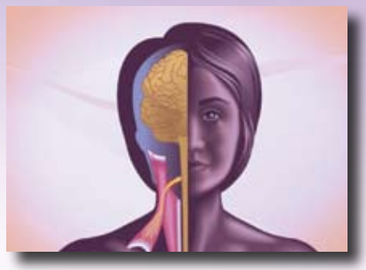
Serious and or immediate allergic reactions have been reported. These reactions include itchy rash, swelling, and shortness of breath. Tell your doctor or get medical help right away if you experience any such symptoms; further injection of BOTOX® or BOTOX® Cosmetic should be discontinued.

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 neck 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 and is believed to block signals that cause neck pain.



As a result, muscle spasms may stop or be greatly reduced, resulting in relief, which may last up to 3 months.[1]

www.BOTOXMedical.com

What to expect from your BOTOX® treatment

Once you and your doctor have determined that BOTOX® (onabotulinumtoxinA) 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 experience pain, infection, inflammation, tenderness, swelling, redness and/or bleeding/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.[1]

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

IMPORTANT SAFETY INFORMATION (continued)
Do not take BOTOX® or BOTOX® Cosmetic if you: are allergic to any of the ingredients in BOTOX® or BOTOX® Cosmetic (see Medication Guide for ingredients); had an allergic reaction to any other botulinum toxin product such as *Myobloc*® or *Dysport*®; have a skin infection at the planned injection site.

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.[1]

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

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Frequently asked questions about BOTOX® treatment

Does BOTOX® treatment hurt?

The needles used to administer BOTOX® (onabotulinumtoxinA) 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® neurotoxin?

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 approximately 20 years. The same formulation with dosing specific to temporarily treat moderate to severe glabellar lines (moderate to severe frown lines between the brows) for people ages 18 to 65 was approved in 2002 as BOTOX® Cosmetic (onabotulinumtoxinA).

Is it safe to get repeated injections of BOTOX®?

BOTOX® treatment is approved by the FDA for repeat injections. In most patients, BOTOX® treatment typically lasts for up to 3 months[1]—and can be repeated as long as the patient experiences symptom relief and does not have any serious allergic reactions or other side effects related to BOTOX®. Your physician will determine the appropriate time for re-injection. Patients around the world receive repeated injections of BOTOX® neurotoxin to effectively treat a variety of medical conditions (cervical dystonia, blepharospasm, and strabismus).

IMPORTANT SAFETY INFORMATION (continued)

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® or BOTOX® Cosmetic.

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

There are many factors that can impact the results of BOTOX® treatment. A 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.

There are other botulinum toxins available. Are they the same as BOTOX® treatment?

It is important to understand that no two botulinum toxin products are the same. They differ in dosing, manufacturing process, potency, and adverse events. As a result, each product and its Unit dosing is unique and different, and one product cannot take the place of another.

How do I know that I am receiving BOTOX® treatment and not a different product?

BOTOX® neurotoxin is a registered trademark of Allergan, Inc. The BOTOX® product is packaged in a glass vial with a purple or orange 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.

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BOTOX® treatment and your insurance coverage

BOTOX® Reimbursement Solutions

Many insurance plans, including Medicare and Medicaid, cover the cost of BOTOX® (onabotulinumtoxinA) 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, ET.

IMPORTANT SAFETY INFORMATION (continued)
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; are pregnant or plan to become pregnant (it is not known if BOTOX® or BOTOX® Cosmetic can harm your unborn baby); are breast-feeding or plan to breastfeed (it is not known if BOTOX® or BOTOX® Cosmetic passes into breast milk).

BOTOX PATIENT ASSISTANCE® Program

The BOTOX PATIENT ASSISTANCE® Program is dedicated to helping financially eligible patients receive the BOTOX® (onabotulinumtoxinA) treatment they need. There are certain financial and other requirements that you must meet in order to qualify for the program. You may qualify 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
- Meet or be below a certain household income level
- 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 us at BOTOXReimbursementSolutions.com, or call us at 1-800-44-BOTOX, Option 4.

Cervical dystonia and BOTOX® (onabotulinumtoxinA) treatment

Cervical dystonia definition and symptoms

Cervical dystonia is a condition that causes the muscles in your neck to tighten or spasm without your control.[3,4] 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 activities you enjoyed before your symptoms started.

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 tightness[4,5]
- Uncomfortable *pulling* or *drawing* in the neck[6] or head turning[5,7]
- Neck pain (reported in up to 91% of patients)[8]
- Aches and pains around the neck that worsen over time[7]
- Head or hand tremors[5-7]
- Symptoms that progress to involve adjacent body parts[9]

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

BOTOX® and BOTOX® Cosmetic may cause loss of strength or general muscle weakness, or vision problems. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.**

Cervical dystonia and BOTOX® (onabotulinumtoxinA) treatment (continued)

Diagnosing cervical dystonia

Diagnosing cervical dystonia can be a challenge, especially in its early or mild stages. 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.[7]

In testing for cervical dystonia, many different tests may be used including brain imagings, blood tests, EEGs, EMGs, and video monitoring, among others. An evaluation may also include genetic testing in some situations.[4] 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 questions[10]:

- *Do you find your head turning, tilting, or shifting in any direction?*
- *Does your head shake or jerk?*
- *Do your shoulders lift or pull up or down without your control?*
- *Have other people told you that your head pulls to either side, forward, or backward?*
- *Have other people told you that you have head tremors?*
- *Do you have any pain or stiffness in your neck most of the time?*
- *Is there a position you can put your head in to make the movement or pain stop?*
- *Did you ever see a doctor about head turning or shaking?*

Cervical dystonia is a progressive disease

Cervical dystonia is a progressive disease, meaning that the symptoms may get worse with time. In up to approximately 20% of patients, cervical dystonia symptoms go away completely.[9] This is known as remission. However, it is important to understand that the symptoms often return.[9] For most people with cervical dystonia, their symptoms usually stop worsening after 5 years.[9]

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 (continued)
Other side effects of BOTOX® and BOTOX® Cosmetic include: dry mouth, discomfort or pain at the injection site, tiredness, headache, neck pain, and eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.

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 or call 1-800-FDA-1088.

Full Product Information, including Medication Guide, has been provided to your doctor.

Cervical dystonia and BOTOX® (onabotulinumtoxinA) treatment (continued)

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 interferes with a patient's ability to perform activities of daily living.[7]

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.

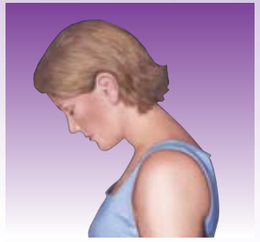
IMPORTANT SAFETY INFORMATION (continued)
BOTOX® and BOTOX® Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems any time (hours to weeks) after injection of BOTOX® or BOTOX® Cosmetic:

- **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

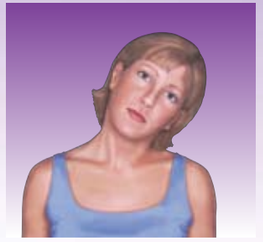
Types of cervical dystonia

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.

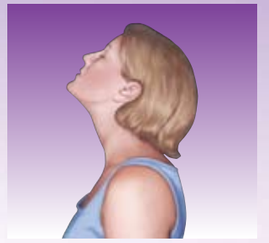
There are 4 main types of cervical dystonia, defined by which way the head is tilting:



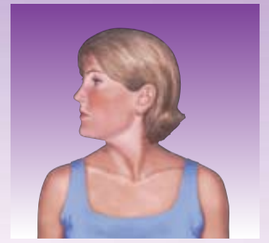
Forward
Anterocollis



To the side
Laterocollis



Backward
Retrocollis



Rotated
Torticollis

Most patients (up to 81%) have a combination of these postures.[5] For example, the head may be pulled in 2 or more directions at the same time, such as forward and to the side.[5] Cervical dystonia may also be called *spasmodic,* if there are sudden, involuntary muscle contractions, or *sustained,* if the muscle tension is continuous.[4]

Cervical dystonia and BOTOX® (onabotulinumtoxinA) treatment (continued)

Treatments for cervical dystonia

Doctors have a number of options for treating cervical dystonia. The most commonly chosen treatment is BOTOX® (onabotulinumtoxinA) neurotoxin. BOTOX® is considered a first-line therapy for cervical dystonia,[11] 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. Oral prescription drugs may also be used. Surgery on the involved nerves may also be an option, but surgery is rarely used, now that BOTOX® neurotoxin is available.[4]

IMPORTANT SAFETY INFORMATION (continued)
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® or BOTOX® Cosmetic:

- **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

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

The dose of BOTOX® is not the same as, or comparable to, another botulinum toxin product.

How BOTOX® can help

For the vast majority of people with cervical dystonia, BOTOX® (onabotulinumtoxinA) injections are very effective. BOTOX® therapy may stop or greatly reduce 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.[7] Another study showed that neck pain relief may happen even before muscle spasms are significantly reduced.[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.[1] 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

With BOTOX® treatment, many cervical dystonia patients get relief from their overly active or tense neck muscles. BOTOX® may also decrease their neck pain associated with cervical dystonia even before muscle spasms are significantly reduced.

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® (onabotulinumtoxinA) injections

IMPORTANT SAFETY INFORMATION (continued)

Serious and or immediate allergic reactions have been reported. These reactions include itchy rash, swelling, and shortness of breath. Tell your doctor or get medical help right away if you experience any such symptoms; further injection of BOTOX® or BOTOX® Cosmetic should be discontinued.

"Occasionally, my neck might grab for a second…and then it just releases. It just doesn't have that power anymore."

Individual results may vary.

www.BOTOXMedical.com

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:

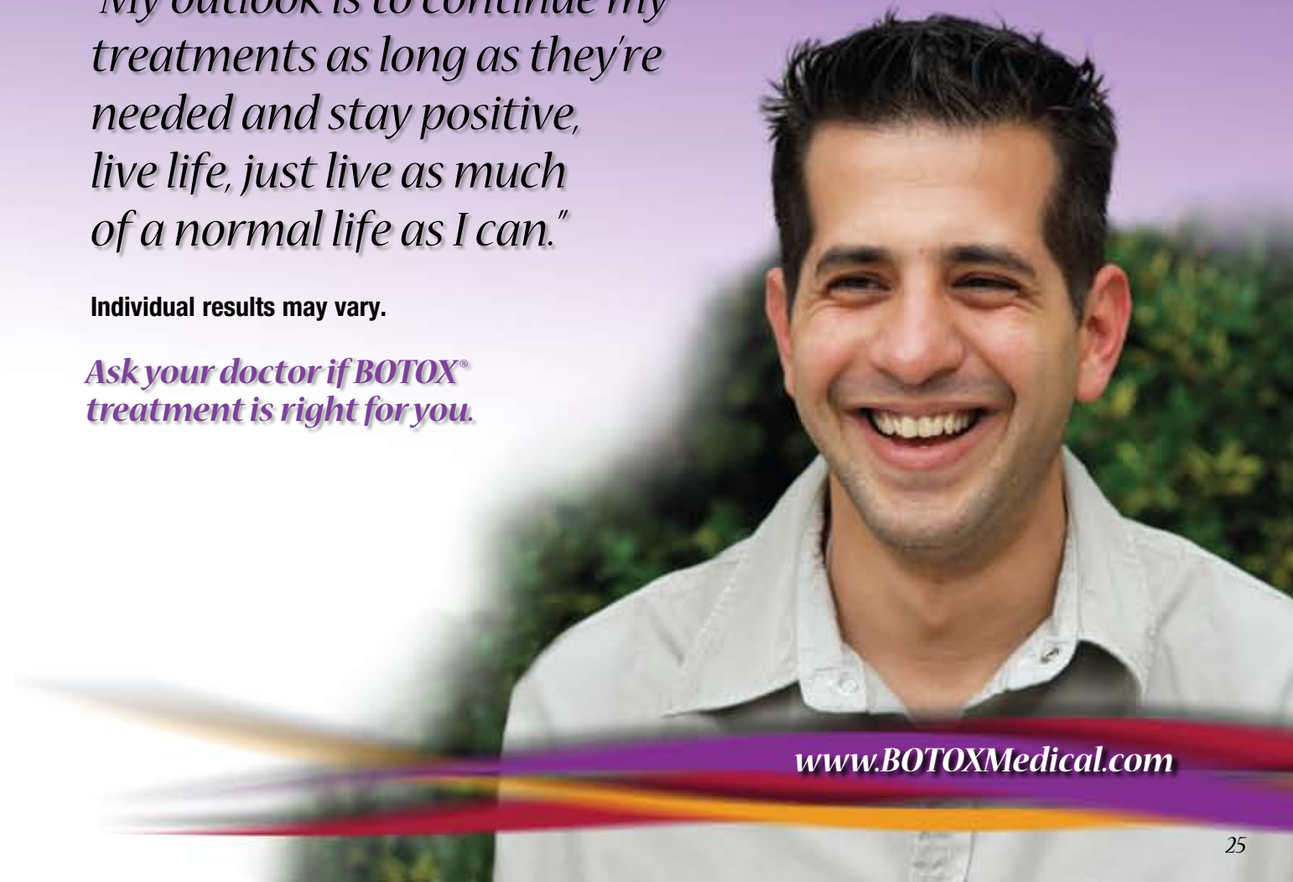
BOTOX® (onabotulinumtoxinA) injections and physical therapy

IMPORTANT SAFETY INFORMATION (continued)
Do not take BOTOX® or BOTOX® Cosmetic if you: are allergic to any of the ingredients in BOTOX® or BOTOX® Cosmetic (see Medication Guide for ingredients); had an allergic reaction to any other botulinum toxin product such as *Myobloc*® or *Dysport*®; have a skin infection at the planned injection site.

"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."

Individual results may vary.

Ask your doctor if BOTOX® treatment is right for you.



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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 help 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 dystonia*[12]
- Make sure you get enough relaxation time[12]
- Eat sensibly and nutritionally
  - *Avoid those foods that stimulate the nerves. Caffeine, sugar, and chocolate can sometimes activate cervical dystonia symptoms*[12]
- Consult with your doctor regarding an exercise program
  - *Light yoga, simple calisthenics, water exercises, and deep breathing exercises can help relax both mind and body*[12]
- Connect with support groups in your area for additional resources and education (some are listed at the back of this brochure)

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.

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

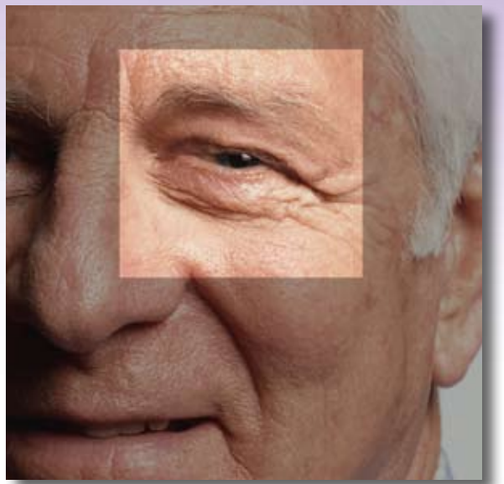
Cervical dystonia is the most common focal dystonia that responds to *sensory tricks.* For example, patients with cervical dystonia may place their hand on the side of their face, chin, or back of the head. This may help reduce the intensity of the symptoms. Lightly touching or applying pressure to certain 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.

IMPORTANT SAFETY INFORMATION (continued)

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® or BOTOX® Cosmetic.

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; are pregnant or plan to become pregnant (it is not known if BOTOX® or BOTOX® Cosmetic can harm your unborn baby); are breast-feeding or plan to breastfeed (it is not known if BOTOX® or BOTOX® Cosmetic passes into breast milk).

Blepharospasm and BOTOX® treatment



Blepharospasm definition 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.[13,14] One serious consequence of blepharospasm is impairment of vision. In some patients, forced closure of the eyelid becomes so severe that doing simple things such as driving a car or using a computer becomes a challenge. Approximately 65% of people with blepharospasm are female, and the average age of onset is 56 years.[14]

IMPORTANT SAFETY INFORMATION (continued)
Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal products.

BOTOX® and BOTOX® Cosmetic may cause loss of strength or general muscle weakness, or vision problems. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.**

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.[13,14]

As blepharospasm progresses, blinking usually becomes more frequent, forceful, and uncontrollable. Bright light, noise, stress, polluted air, or wind can make the symptoms worse.[13] Without proper medical treatment, few blepharospasm patients get better on their own.[14]

Early symptoms of blepharospasm may include[14]:

- Dry eyes or watering eyes
- Light sensitivity
- Increased blinking
- Ocular pain
- Soreness

How BOTOX® treatment can help

BOTOX® (onabotulinumtoxinA) neurotoxin has been the principal treatment for blepharospasm since FDA approval in 1989. BOTOX® injections are administered directly into the site of action. 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.[1]

Strabismus and BOTOX® treatment

Strabismus definition 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.[15] 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), eyeglasses, and/or contact lenses.[15] In some cases where strengthening techniques are not successful, surgery may be required to realign the eye muscles.[15]

IMPORTANT SAFETY INFORMATION (continued)
Other side effects of BOTOX® and BOTOX® Cosmetic include: dry mouth, discomfort or pain at the injection site, tiredness, headache, neck pain, and eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.

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 or call 1-800-FDA-1088.

Full Product Information, including Medication Guide, has been provided to your doctor.

Strabismus in adults is often diagnosed in those who were untreated or unsuccessfully treated during childhood.[16] There are also some adults who develop strabismus due to illness or trauma, which usually results in double vision or a limitation in their depth perception or field of vision (peripheral and side).[16]

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 4 to 6, strabismus can lead to permanent loss of sight in the deviating eye.[15]

How BOTOX® treatment can help

In treating strabismus, only BOTOX® (onabotulinumtoxinA) treatment is believed to have an effect on pairs of muscles. Upon being injected with BOTOX® neurotoxin, the muscles weaken and spasms are slightly reduced. This allows the muscles on the other side of the eye to contract.[1] Through this dual action, BOTOX® treatment is thought to help the eyes align, or look in the same direction.

Finding a doctor who injects BOTOX®

If you would like to discuss your condition with a doctor who injects BOTOX® (onabotulinumtoxinA), you can find one by visiting www.BOTOXMedical.com and using our Find a Doctor tool.

To locate a doctor who injects BOTOX® neurotoxin, simply visit these websites:

The official BOTOX® website:

www.BOTOXMedical.com

WebMD® Physician Directory:

http://doctor.webmd.com/physician_finder

AMA DoctorFinder:

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

Please see Important Safety Information about BOTOX® on front cover and throughout brochure.

For more information on BOTOX®, visit our website at

www.BOTOXMedical.com

or call

1-800-44-BOTOX

BOTOX® onabotulinumtoxinA

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.

Many national organizations have local chapters. Please contact the national group for more information on 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

*The organizations listed are provided as potential resources for patients and caregivers; they are not endorsed by Allergan.

For more information on BOTOX®, visit our website at

www.BOTOXMedical.com

or call 1-800-44-BOTOX

Please see Important Safety Information about BOTOX® on front cover and inside brochure.

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ALLERGAN

BOTOX® onabotulinumtoxinA

BOTOX® Cosmetic (onabotulinumtoxinA) for injection

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

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of **BOTOX® Cosmetic** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.

DESCRIPTION

BOTOX® Cosmetic (onabotulinumtoxinA) for injection, 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, intended for intramuscular use. 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-drying.

One Unit of **BOTOX® Cosmetic** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to Allergan's product, **BOTOX® Cosmetic**. 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 **BOTOX® Cosmetic** cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. In addition, 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® Cosmetic** is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX® Cosmetic** contains either 100 Units of *Clostridium botulinum* type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride or 50 Units of *Clostridium botulinum* type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

CLINICAL PHARMACOLOGY

BOTOX® Cosmetic blocks neuromuscular transmission by binding to acceptor sites on motor 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® Cosmetic** 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® Cosmetic**.

Pharmacokinetics

Using currently available analytical technology, it is not possible to detect **BOTOX® Cosmetic** in the peripheral blood following intramuscular injection at the recommended doses.

CLINICAL STUDIES

Glabellar Lines

Two phase 3 randomized, multi-center, double-blind, placebo-controlled studies of identical design were conducted to evaluate **BOTOX® Cosmetic** for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. The studies enrolled healthy adults (ages 18 to 75) with glabellar lines of at least moderate severity at maximum frown. Patients were excluded if they had ptosis, deep dermal scarring, or an inability to substantially lessen glabellar lines even by physically spreading them apart. Subjects received a single treatment with **BOTOX® Cosmetic** (N=405, combined studies) or placebo (N=132, combined studies). Injection volume was 0.1 mL/injection site, for a dose/injection site in the active treatment groups of 4 Units. Subjects were injected intramuscularly in five sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units.

The co-primary efficacy endpoints were the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change in appearance of glabellar lines, both at Day 30 post-injection. For the investigator rating, using a 4-point grading scale (0=none, 3=severe) a responder was defined as having a severity grade of 0 or 1. For the subject's global assessment of change, the ratings were from +4 (complete improvement) to -4 (very marked worsening). A responder was defined as having a grade of at least +2 (moderate improvement). After completion of the randomized studies, subjects were offered participation in an open label, repeat treatment study to assess the safety of repeated treatment sessions.

The combined results of these two efficacy trials are presented here. The mean age was 46 years, with 32 patients (6%) ≥ 65 years of age. Most of the subjects (82%) were women, and Caucasian (84%). At baseline, 210 patients (39%) had glabellar line severity scores at rest of moderate or severe.

In these studies, the severity of glabellar lines was reduced for up to 120 days in the **BOTOX® Cosmetic** group compared to the placebo group as measured both by investigator rating of glabellar line severity at maximum frown (Table 1), and by subject's global assessment of change in appearance of glabellar lines (Table 2).

TABLE 1.
Investigator's Assessment of Glabellar Line Severity at Maximum Frown – Responder Rates (% and Number of Subjects with Severity of None or Mild)

Day	BOTOX® Cosmetic	Placebo	Difference[a]
7	74% 299/405	6% 8/132	68% (62, 74)
30[b]	80% 325/405	3% 4/132	77% (72, 82)
60	70% 283/403	2% 2/130	69% (64, 74)
90	48% 192/403	2% 3/128	45% (40, 51)
120	25% 102/403	2% 2/128	24% (19, 29)

[a] 95% confidence intervals are shown in parenthesis
[b] Day 30: Co-Primary Efficacy Time point, P<0.001

TABLE 2.
Subject's Assessment of Change in Appearance of Glabellar Lines – Responder Rates (% and Number of Subjects with at Least Moderate Improvement)

Day	BOTOX® Cosmetic	Placebo	Difference[a]
7	82% 334/405	9% 12/132	73% (68, 80)
30[b]	89% 362/405	7% 9/132	83% (77, 88)
60	82% 330/403	4% 5/130	78% (73, 83)
90	63% 254/403	3% 4/128	60% (54, 66)
120	39% 157/403	1% 1/128	38% (33, 43)

[a] 95% confidence intervals are shown in parenthesis
[b] Day 30: Co-Primary Efficacy Time point, P<0.001

In the subset of patients with resting severity scores of moderate or severe, the investigator assessment of a resting severity of mild or none at day 30 was also achieved by more **BOTOX® Cosmetic** treated patients (74%, 119/161) than placebo treated patients (20%, 10/49).

Analysis of the limited number of patients 65 years or older suggested a lower treatment-associated response compared to patients less than 65 years of age. (Table 3).

TABLE 3.
Investigator's and Subject's Assessment – Responder Rates for Subjects < 65 and ≥ 65 Years of Age at Day 30

Assessment	Age Group	BOTOX® Cosmetic N=405	Placebo N=132	Difference[a]
Investigators (maximal frown)	< 65	83% 316/382	2% 2/123	81% (77, 86)
Subjects	< 65	91% 346/382	7% 8/123	84% (79, 90)
Investigators (maximal frown)	≥ 65	39% 9/23	22% 2/9	17% (-17, 51)
Subjects	≥ 65	70% 16/23	11% 1/9	58% (31, 86)

[a] 95% confidence intervals are shown in parenthesis

Exploratory analyses by gender suggested that responder rates in the **BOTOX® Cosmetic** treated group were higher for women than for men for both the investigator assessment (day 30; 85% of 334 women, 59% of 71 men) and the Subject Assessment (day 30; 93% of women, 72% of men). In the limited number of non-Caucasian patients (n=64 in the **BOTOX® Cosmetic** treated group) the responder rates were similar to those observed in the Caucasian patients.

INDICATIONS AND USAGE

BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

CONTRAINDICATIONS

BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

WARNINGS

BOTOX® and **BOTOX® Cosmetic** contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® Cosmetic**.

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

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX® Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® Cosmetic cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method (see DESCRIPTION).

Spread of Toxin Effect

Postmarketing safety data from **BOTOX® Cosmetic** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX®/BOTOX® Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX®** for blepharospasm at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **BOTOX® Cosmetic** should be discontinued and appropriate medical therapy immediately instituted. 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.

Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX® Cosmetic** (see **ADVERSE REACTIONS**).

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX®** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved (see **WARNINGS**).

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin (see **WARNINGS, ADVERSE REACTIONS, CLINICAL PHARMACOLOGY**).

Cardiovascular System

There have been reports following administration of **BOTOX®** of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

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® Cosmetic** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX® Cosmetic** must understand the relevant neuromuscular and/or orbital anatomy of the area involved, as well as any alterations to the anatomy due to prior surgical procedures and avoid injection into vulnerable anatomic areas.

Caution should be used when **BOTOX® Cosmetic** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

Reduced blinking from **BOTOX® Cosmetic** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of **BOTOX®** for the treatment of blepharospasm, one case of corneal perforation in an aphakic eye 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.

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.

Caution should be used when **BOTOX® Cosmetic** treatment is used in patients who have an inflammatory skin problem at the injection site, marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart as these patients were excluded from the Phase 3 safety and efficacy trials.

Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Injection intervals of **BOTOX® Cosmetic** should be no more frequent than every three months and should be performed using the lowest effective dose (see **ADVERSE REACTIONS, IMMUNOGENICITY**).

Information for Patients

The physician should provide a copy of the FDA-Approved Patient Medication Guide and review the contents with the patient. Patients should be advised to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens.

Patients should be counseled that if loss of strength, muscle weakness, or impaired vision occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Drug Interactions

Co-administration of **BOTOX® Cosmetic** and aminoglycosides[1] or other agents interfering with neuromuscular transmission (e.g., curare-like nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, anticholinesterases, succinylcholine chloride) 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

Administration of **BOTOX® Cosmetic** is not recommended during pregnancy. There are no adequate and well-controlled studies of **BOTOX® Cosmetic** in pregnant women. When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of **BOTOX® Cosmetic** was 4 Units/kg. Higher doses (8 Units/kg or 16 Units/kg) were associated with reductions in fetal body weights and/or delayed ossification.

In a range finding study in rabbits, daily injection of 0.125 Units/kg/day (days 6 to 18 of gestation) and 2 Units/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to **BOTOX® Cosmetic**.

If the patient becomes pregnant after the administration of this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations that 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® Cosmetic**.

The reproductive NOEL following intramuscular injection of 0, 4, 8, and 16 Units/kg was 4 Units/kg in male rats and 8 Units/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 testicular atrophy or 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® Cosmetic** is administered to a nursing woman.

Pediatric Use

Use of **BOTOX® Cosmetic** is not recommended in children.

Geriatric Use

The two clinical studies of **BOTOX® Cosmetic** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, the responder rates appeared to be higher for patients younger than age 65 than for patients 65 years or older (see **CLINICAL STUDIES**).

There were too few patients (N=3) over the age of 75 to allow any meaningful comparisons.

ADVERSE REACTIONS

General

BOTOX® and **BOTOX® Cosmetic** contain the same active ingredient in the same formulation. Therefore adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX® Cosmetic**.

The most serious adverse events reported after treatment with botulinum toxin include spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, pneumonia, and/or other significant debility.

There have also been 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 pre-existing cardiovascular disease (see **WARNINGS**).

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, 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.

In general, adverse events occur within the first week following injection of **BOTOX® Cosmetic** and while generally transient may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema and/or bleeding/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.

Glabellar Lines

In clinical trials of **BOTOX® Cosmetic** the most frequently reported adverse events following injection of **BOTOX® Cosmetic** were headache*, respiratory infection*, flu syndrome*, blepharoptosis and nausea.

Less frequently occurring (<3%) adverse reactions included pain in the face, erythema at the injection site*, paresthesia* and muscle weakness. While local weakness of the injected muscle(s) is representative of the expected pharmacological action of botulinum toxin, weakness of adjacent muscles may occur as a result of the spread of toxin. These events are thought to be associated with the injection and occurred within the first week. The events were generally transient but may last several months or longer.
(* incidence not different from Placebo)

The data described in Table 4 reflect exposure to **BOTOX® Cosmetic** in 405 subjects aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of **BOTOX® Cosmetic** in the improvement of the appearance of glabellar lines (see **CLINICAL STUDIES**). Adverse events of any cause were reported for 44% of the **BOTOX® Cosmetic** treated subjects and 42% of the placebo treated subjects. The incidence of blepharoptosis was higher in the **BOTOX® Cosmetic** treated arm than in placebo (3% vs. 0).

In the open-label, repeat injection study, blepharoptosis was reported for 2% (8/373) of subjects in the first treatment cycle and 1% (4/343) of subjects in the second treatment cycle. Adverse events of any type were reported for 49% (183/373) of subjects overall. The most frequently reported of these adverse events in the open-label study included respiratory infection, headache, flu syndrome, blepharoptosis, pain and nausea.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates 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.

TABLE 4.
Adverse Events Reported at Higher Frequency (>1%) in the BOTOX® Cosmetic Group Compared to the Placebo Group

	Percent of Patients Reporting Adverse Events	
Adverse Events by Body System	**BOTOX® Cosmetic (N=405) %**	**Placebo (N=130) %**
Overall	44	42
Body as a Whole Pain in Face	2	1
Skin and Appendages Skin Tightness	1	0
Digestive System Nausea Dyspepsia Tooth Disorder	 3 1 1	 2 0 0
Special Senses Blepharoptosis	3	0
Musculoskeletal System Muscle Weakness	2	0
Cardiovascular Hypertension	1	0

Immunogenicity

Treatment with **BOTOX® Cosmetic** may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments with **BOTOX® Cosmetic** by inactivating the biological activity of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX® Cosmetic** has not been well studied.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that botulinum toxin 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 the lowest effective dose given at the longest feasible intervals between injections.

Postmarketing Experience

Transient ptosis, the most frequently reported complication, has been reported in the literature in approximately 5% of patients. There has been a single report of diplopia, which resolved completely in three weeks.

The following other adverse reactions have been identified since the drug has been marketed: abdominal pain; blurred vision; brachial plexopathy; decreased hearing; diarrhea; ear noise; erythema multiforme; fever; focal facial paralysis; glaucoma; localized numbness; loss of appetite; malaise; myalgia; myasthenia gravis; pruritus; psoriasiform eruption; retinal vein occlusion; sweating; syncope; vertigo with nystagmus; and vomiting.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to botulinum toxin.

Reporting Adverse Events

Adverse events following use of **BOTOX® Cosmetic** should be reported to the Pharmacovigilance Department, Allergan Inc. (1-800-433-8871). Adverse events may also be reported to the U.S. Department of Health and Human Services (DHHS) Adverse Event Reporting System. Report forms and reporting requirement information can be obtained from Adverse Event Reporting System (AERS) through a toll free number 1-800-822-7967.

Overdosage

Excessive doses of **BOTOX® Cosmetic** may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis (see **WARNINGS** and **PRECAUTIONS**). Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or muscle paralysis.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/ncidod/srp/drugs/drug-service.html.

DOSAGE AND ADMINISTRATION

For Intramuscular Injection Only

BOTOX® Cosmetic is to be reconstituted only with 0.9% sterile, non-preserved saline prior to intramuscular injection. Per the dilution table below, draw up the required amount of 0.9% sterile non-preserved sodium chloride solution into a syringe to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL. The duration of activity of **BOTOX® Cosmetic** for glabellar lines is approximately 3-4 months. The safety and effectiveness of more frequent dosing with **BOTOX® Cosmetic** has not been clinically evaluated and is not recommended.

Dilution Table

Diluent Added to 100 Unit Vial (0.9% Sodium Chloride Injection Only)	Resulting Dose Units per 0.1 mL	Diluent Added to 50 Unit Vial (0.9% Sodium Chloride Injection Only)	Resulting Dose Units per 0.1 mL
2.5 mL	4 Units	1.25 mL	4 Units

Reconstituted **BOTOX® Cosmetic** should be clear, colorless, and free of particulate matter.

BOTOX® Cosmetic is supplied as a single use vial. The product and diluent do not contain a preservative. Once opened and reconstituted it should be stored in a refrigerator (2° to 8°C) and used within 24 hours. Discard any remaining solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not freeze reconstituted **BOTOX® Cosmetic**.

Dilution Technique

Using a 21-gauge needle and an appropriately sized syringe draw up a total of 2.5 mL/100 Unit vial or 1.25 mL/50 Unit vial of 0.9% sterile saline without a preservative. Insert the needle at a 45° angle and slowly inject into the **BOTOX® Cosmetic** vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently rotate the vial and record the date and time of reconstitution on the space on the label.

Draw at least 0.5 mL of the properly reconstituted toxin into the sterile syringe, preferably a tuberculin syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-33 gauge needle. Confirm the patency of the needle.

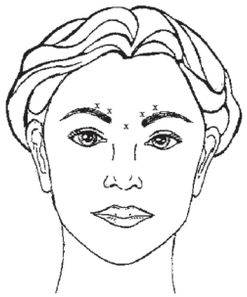
Injection Technique

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected.

In order to reduce the complication of ptosis the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Do not inject toxin closer than 1 cm above the central eyebrow.

Using a 30-33 gauge needle, inject a dose of 0.1 mL into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units. Typically the initial doses of reconstituted **BOTOX® Cosmetic** induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.



HOW SUPPLIED

BOTOX® Cosmetic is supplied in a single use vial in the following sizes:

50 Units: NDC 0023-3919-50
100 Units: NDC 0023-9232-01

Vials of **BOTOX® Cosmetic** 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 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

Rx Only
Single use vial.

Storage

Unopened vials of **BOTOX® Cosmetic** should be stored in a refrigerator (2° to 8°C) for up to 36 months for the 100 Unit vial or up to 24 months for the 50 Unit vial.

Administer **BOTOX® Cosmetic** within 24 hours of reconstitution; during this period reconstituted **BOTOX® Cosmetic** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX® Cosmetic** should be clear, colorless and free of particulate matter.

Do not use after the expiration date on the vial. All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

Revised: 06/2010

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

REFERENCE

1. Wang YC, Burr DH, Korthals GJ, Sugiyama H. Acute toxicity of aminoglycoside antibiotics as an aid in detecting botulism. Appl Environ Microbiol 1984; 48:951-955.

71823US12A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

BOTOX (onabotulinumtoxinA)
Initial U.S. Approval: 1989

WARNING: Distant Spread of Toxin Effect
See full prescribing information for complete boxed warning.
The effects of **BOTOX** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

RECENT MAJOR CHANGES

- Boxed Warning, Distant Spread of Toxin Effect 7/2009
- Indications and Usage, Upper Limb Spasticity (1.1) 3/2010
- Dosage and Administration, Upper Limb Spasticity (2.2) 3/2010
- Warnings and Precautions (5.1, 5.2, 5.4) 7/2009
- Warnings and Precautions (5.3, 5.6, 5.9) 3/2010

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the treatment of:
- Upper limb spasticity in adult patients (1.1)
- Cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.2)
- Severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.3)
- Blepharospasm associated with dystonia in patients ≥12 years of age (1.4)
- Strabismus in patients ≥12 years of age (1.4)

Important limitations:

- Safety and effectiveness of **BOTOX** have not been established for the treatment of upper limb spasticity in pediatric patients, and for the treatment of lower limb spasticity in adult and pediatric patients.
- Safety and effectiveness of **BOTOX** for hyperhidrosis in body areas other than axillary have not been established.

DOSAGE AND ADMINISTRATION

- Indication specific dosage and administration recommendations should be followed; Do not exceed a total dose of 360 Units administered every 12 to 16 weeks or at longer intervals (2)
- See Preparation and Dilution Technique for instructions on **BOTOX** reconstitution, storage, and preparation before injection (2.1)
- Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.2)
- Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients (2.3)
- Axillary hyperhidrosis: 50 Units per axilla (2.4)
- Blepharospasm: 1.25 Units - 2.5 Units into each of 3 sites per affected eye (2.5)
- Strabismus: 1.25 Units - 2.5 Units initially in any one muscle (2.6)

DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.3, 6.2)
- Infection at the proposed injection site (4.2)

WARNINGS AND PRECAUTIONS

- Potency Units of **BOTOX** not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death (5.2)
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties (5.2, 5.4)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.4, 5.6)
- Corneal exposure and ulceration (5.7)
- Retrobulbar hemorrhages and compromised retinal circulation (5.8)
- Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity (5.9)

ADVERSE REACTIONS

In controlled studies, the most commonly observed adverse reactions (≥ 5% and > placebo) were:
- Spasticity: pain in extremity (6.1)
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis (6.1)
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Patients receiving concomitant treatment of **BOTOX** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of **BOTOX** may be potentiated (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the treatment of upper limb spasticity and axillary hyperhidrosis, in patients under 16 years of age for the treatment of cervical dystonia, and in patients under 12 years of age for the treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

Distant Spread of Toxin Effect
Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

1 INDICATIONS AND USAGE

1.1 Upper Limb Spasticity

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Important limitations
Safety and effectiveness of **BOTOX** have not been established for the treatment of other upper limb muscle groups, or for the treatment of lower limb spasticity. Safety and effectiveness of **BOTOX** have not been established for the treatment of spasticity in pediatric patients under age 18 years. **BOTOX** has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with **BOTOX** is not intended to substitute for usual standard of care rehabilitation regimens.

1.2 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.3 Primary Axillary Hyperhidrosis

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

Important limitations
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. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of **BOTOX®** have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.4 Blepharospasm and Strabismus

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.

2 DOSAGE AND ADMINISTRATION

The potency Units of **BOTOX** (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of **BOTOX** cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Warnings and Precautions (5.1) and Description (11)]*.

Injection specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

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 and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for treatment of strabismus and of upper limb spasticity, and may be useful for the treatment of cervical dystonia.

Use caution when **BOTOX** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

2.1 Preparation and Dilution Technique

BOTOX is supplied in single-use 100 Units and 200 Units per vial. Prior to injection, reconstitute each vacuum-dried vial of **BOTOX** with sterile, non-preserved 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (Dilution Table), 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 24 hours after reconstitution. During this time period, reconstituted **BOTOX** should be stored in a refrigerator (2° to 8°C).

Dilution Table: 0.9% Sodium Chloride Injection Dilution Instructions for 100 Unit and 200 Unit BOTOX Vials

Diluent* Added to **100 Unit** Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to **200 Unit** Vial	Resulting Dose Units per 0.1 mL
1 mL	10 Units	1 mL	20 Units
2 mL	5 Units	2 mL	10 Units
4 mL	2.5 Units	4 mL	5 Units
8 mL	1.25 Units	8 mL	2.5 Units
		10 mL	2 Units

*0.9% Sodium Chloride Injection Only

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).

An injection of **BOTOX** is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin 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**.

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.

2.2 Upper Limb Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with **BOTOX**.

In clinical trials, doses ranging from 75 Units to 360 Units were divided among selected muscles at a given treatment session.

Following are recommended dose ranges per muscle:

	Total Dosage (Number of Sites)
Biceps Brachii	100 Units - 200 Units divided in 4 sites
Flexor Carpi Radialis	12.5 Units - 50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units - 50 Units in 1 site
Flexor Digitorum Profundus	30 Units - 50 Units in 1 site
Flexor Digitorum Sublimis	30 Units - 50 Units in 1 site

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with 0.9% non-preserved sterile saline (see Dilution Table). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) 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 or nerve stimulation techniques is recommended.

Repeat **BOTOX** treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of **BOTOX** and muscles to be injected.

2.3 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 of 198 Units to 300 Units). The **BOTOX** dose was divided among the affected muscles *[see Clinical Studies (14.2)]*. 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 muscle to 100 Units or less may decrease the occurrence of dysphagia *[see Warnings and Precautions (5.2, 5.4, 5.5)]*.

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with 0.9% non-preserved sterile saline, depending on volume and number of injection sites desired to achieve treatment objectives (see Dilution Table). In general, no more than 50 Units per site should be administered. An appropriately sized needle (e.g., 25-30 gauge) 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.

2.4 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 Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Dilution Table). 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.

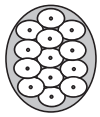
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

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.

2.5 Blepharospasm

For blepharospasm, reconstituted **BOTOX** is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units - 2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal 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.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Dilution Table).

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 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, and is rare to have the effect be permanent.

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

2.6 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** injected for treatment of strabismus should be between 0.05 - 0.15 mL per muscle.

The initial listed doses of the reconstituted **BOTOX** *[see Dosage and Administration (2.1)]* typically create paralysis of the 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 Units - 2.5 Units in any one muscle.
   - B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units - 5 Units in any one muscle.
   - C. For persistent VI nerve palsy of one month or longer duration: 1.25 Units - 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.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Dilution Table).

3 DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection *[see Dosage and Administration (2.1)]*.

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions (5.3)]*.

4.2 Infection at the Injection Site(s)
BOTOX® is contraindicated in the presence of infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products
The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

5.2 Spread of Toxin Effect
Postmarketing safety data from **BOTOX** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX/BOTOX Cosmetic** at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX** for blepharospasm at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported.

5.3 Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **BOTOX** should be discontinued and appropriate medical therapy immediately instituted. 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.

5.4 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia
Treatment with **BOTOX** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved *[see Warnings and Precautions (5.2)]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

5.5 Pre-Existing Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX** *[see Adverse Reactions (6.1)]*.

5.6 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity
Patients with compromised respiratory status treated with **BOTOX** for upper limb spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients with stable reduced pulmonary function (defined as FEV1 40-80% of predicted value and FEV1/FVC ≤ 0.75), the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with **BOTOX** than in patients treated with placebo (see Table 1).

Table 1: Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 post-injection with up to two treatment cycles with BOTOX or placebo

	BOTOX 360 Units		**BOTOX 240 Units**		**Placebo**	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX** *[see Warnings and Precautions (5.9)]*.

5.7 Corneal Exposure and Ulceration in Patients Treated with BOTOX for 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. 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.

5.8 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus
During the administration of **BOTOX** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.9 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with **BOTOX®** (3% at 251 Units - 360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX** (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%).

5.10 Human Albumin and Transmission of Viral Diseases
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) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

6 ADVERSE REACTIONS

The following adverse reactions to **BOTOX** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:
- Spread of Toxin Effects *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Contraindications (4.1) and Warnings and Precautions (5.3)]*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *[see Warnings and Precautions (5.4)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

BOTOX and **BOTOX Cosmetic** contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX Cosmetic** also have the potential to be observed with the use of **BOTOX** and vice-versa.

In general, adverse events occur within the first week following injection of **BOTOX** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.2)]*.

Upper Limb Spasticity
Table 2 below lists the adverse reactions reported by ≥ 2% of **BOTOX**-treated patients and more frequent than in placebo-treated patients in double-blind, placebo-controlled clinical trials.

Table 2: Adverse Reactions Reported by ≥ 2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	**BOTOX** 251 Units - 360 Units (N=115)	**BOTOX** 150 Units - 250 Units (N=188)	**BOTOX** <150 Units (N=54)	**Placebo** (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4 (3%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (3%)	4 (2%)	0	2 (1%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7 (6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

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%).

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.

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 *[see Warnings and Precautions (5.2, 5.4)]*.

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 and Precautions (5.2, 5.4)]*. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms *[see Warnings and Precautions (5.4)]*.

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.

Primary Axillary Hyperhidrosis
The most frequently reported adverse events (3 - 10% of adult 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 **BOTOX** 50 Units and 110 patients exposed to **BOTOX** 75 Units in each axilla.

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 (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, 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, reduced blinking from **BOTOX®** injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. 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 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 was 17%.

The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Post-Marketing Experience
There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.3, 5.4)]*.

There have also been 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.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events, not already addressed elsewhere in the package insert, have been reported since the drug has been marketed: abdominal pain; anorexia; brachial plexopathy; diarrhea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; myalgia; paresthesia; pyrexia; radiculopathy; skin rash (including erythema multiforme, and psoriasiform eruption); tinnitus; vertigo; visual disturbances; and vomiting.

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to botulinum toxin.

6.3 Immunogenicity
As with all therapeutic proteins, there is a potential for 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.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of **BOTOX**, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to **BOTOX** therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to **BOTOX** therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%) and two patients among the 380 adult upper limb spasticity patients (0.5%) 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** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. 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** 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.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with **BOTOX** (onabotulinumtoxinA) for injection.

Co-administration of **BOTOX** and aminoglycosides 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.

Use of anticholinergic drugs after administration of **BOTOX** may potentiate systemic anticholinergic effects.

The effect of administering different botulinum neurotoxin products 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.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX**.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category C.
There are no adequate and well-controlled studies in pregnant women. **BOTOX** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When **BOTOX** (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 1½ times the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

When **BOTOX** was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the average high human dose based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 3 times the average high human dose based on Units/kg.

8.3 Nursing Mothers
It is not known whether **BOTOX** 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.

8.4 Pediatric Use
Spasticity
Safety and effectiveness of **BOTOX®** for the treatment of spasticity have not been established in patients below the age of 18 years.

Cervical Dystonia
Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Axillary Hyperhidrosis
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 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, dose 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.

10 OVERDOSAGE

Excessive doses of **BOTOX** (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis *[see Boxed Warning and Warnings and Precautions (5.2, 5.4)]*. Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

11 DESCRIPTION

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain Clostridium botulinum type A, and intended for intramuscular and intradermal use. 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-drying.

One Unit of **BOTOX** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) 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 **BOTOX** 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 preclude 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 either 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride; or 200 Units of Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
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.

12.3 Pharmacokinetics
Using currently available analytical technology, it is not possible to detect **BOTOX** in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Long term studies in animals have not been performed to evaluate the carcinogenic potential of **BOTOX**.

Mutagenesis
BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicologic assays.

Impairment of Fertility
In fertility studies of **BOTOX** (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

14 CLINICAL STUDIES

14.1 Upper Limb Spasticity
The efficacy and safety of **BOTOX** for the treatment of upper limb spasticity were evaluated in three randomized, multi-center, double-blind, placebo-controlled studies.

Study 1 included 126 patients (64 **BOTOX**® and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. **BOTOX** (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 3). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 3: Study Medication Dose and Injection Sites in Study 1

Muscles Injected	Volume (mL)	BOTOX (Units)	Number of Injection Sites
Wrist Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
Finger Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
Thumb Adductor Pollicis[a]	0.4	20	1
Flexor Pollicis Longus[a]	0.4	20	1

[a] injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Possible scores range from 0 to 4:
0 = No increase in muscle tone (none)
1 = Slight increase in muscle tone, giving a 'catch' when the limb was moved in flexion or extension (mild)
2 = More marked increase in muscle tone but affected limb is easily flexed (moderate)
3 = Considerable increase in muscle tone - passive movement difficult (severe)
4 = Limb rigid in flexion or extension (very severe).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 4.

Table 4: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

	BOTOX (N=64)	Placebo (N=62)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[a]	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale†††[b]	-1.0*	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale†††[c]	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment†††	2.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo (p≤0.05)
[a] **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[b] **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[c] **BOTOX** injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of **BOTOX** with placebo and included 91 patients [**BOTOX** 360 Units (N=21), **BOTOX** 180 Units (N=23), **BOTOX** 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. **BOTOX** and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 5).

Table 5: Study Medication Dose and Injection Sites in Study 2 and Study 3

	Total Dosage				
Muscles Injected	**BOTOX low dose (90 Units)**	**BOTOX mid dose (180 Units)**	**BOTOX high dose (360 Units)**	**Volume (mL) per site**	**Injection Sites (n)**
Wrist Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
Finger Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
Elbow Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 6.

Table 6: Primary and Key Secondary Endpoints by Muscle Group and BOTOX® Dose at Week 6 in Study 2

	BOTOX low dose (90 Units) (N=21)	BOTOX mid dose (180 Units) (N=23)	BOTOX high dose (360 Units) (N=21)	Placebo (N=26)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[b]	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††[c]	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††[d]	-0.5	-1.0*	-0.5[a]	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo (p≤0.05)
[a] p=0.053
[b] Total dose of **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of **BOTOX** injected into biceps brachii muscle

Study 3 compared 3 doses of **BOTOX** with placebo and enrolled 88 patients [**BOTOX** 360 Units (N=23), **BOTOX** 180 Units (N=23), **BOTOX** 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. **BOTOX** and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 5).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 7.

Table 7: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

	BOTOX low dose (90 Units) (N=23)	BOTOX mid dose (180 Units) (N=21)	BOTOX high dose (360 Units) (N=22)	Placebo (N=19)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†[b]	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††[c]	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale†[d]	-0.5	-0.5	-1.0*	-0.5

† Primary endpoint at Week 4
†† Secondary endpoints at Week 4
* Significantly different from placebo (p≤0.05)
[b] Total dose of **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of **BOTOX** injected into biceps brachii muscle

14.2 Cervical Dystonia

A phase 3 randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. 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 Physician 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 8.

Table 8: 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]
% Patients with Any Improvement on Physician 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. 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 Units 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 9. The total dose and muscles selected were tailored to meet individual patient needs.

Table 9: 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.

14.3 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 two **BOTOX** doses (see Table 10).

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 either 50 Units of **BOTOX** (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the **BOTOX** group and 36% (28/78) in the placebo group, $p < 0.001$. The difference in percentage of responders between **BOTOX** and placebo was 55% (95% CI = 43.3, 65.9).

Table 10: 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% CI)
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.

14.4 Blepharospasm
Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of **BOTOX** at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was 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, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 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 weeks prior to the need for re-treatment.

14.5 Strabismus
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.

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes:
100 Units NDC 0023-1145-01
200 Units NDC 0023-3921-02

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/lot 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 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

Storage
Unopened vials of **BOTOX** should be stored in a refrigerator (2° to 8°C) for up to 36 months for the 100 Unit vial or up to 24 months for the 200 Unit vial. Do not use after the expiration date on the vial. Administer **BOTOX** within 24 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.

Rx Only

17 PATIENT COUNSELING INFORMATION

Provide a copy of the Medication Guide and review the contents with the patient.

17.1 Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms
Patients should be advised to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens *[see Boxed Warning and Warnings and Precautions (5.2, 5.4)]*.

17.2 Ability to Operate Machinery or Vehicles
Patients should be counseled that if loss of strength, muscle weakness, blurred vision, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

17.3 Medication Guide

MEDICATION GUIDE
BOTOX® and BOTOX® Cosmetic (Boe-tox) (onabotulinumtoxinA) for Injection

Read the Medication Guide that comes with **BOTOX** or **BOTOX Cosmetic** before you start using it and each time it is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

BOTOX® and BOTOX® Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

- **Problems swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.
- People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
  - loss of strength and muscle weakness all over the body
  - double vision
  - blurred vision and drooping eyelids
  - hoarseness or change or loss of voice (dysphonia)
  - trouble saying words clearly (dysarthria)
  - loss of bladder control
  - trouble breathing
  - trouble swallowing

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

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

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines.

What are BOTOX and BOTOX Cosmetic?

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

- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX® Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary).

It is not known whether **BOTOX** is safe or effective in children younger than:

- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

Who should not take BOTOX or BOTOX Cosmetic?

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc®* or *Dysport®*
- have a skin infection at the planned injection site

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?

Tell your doctor about all your medical conditions, including if you have:

- a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- a breathing problem, such as asthma or emphysema
- swallowing problems
- bleeding problems
- plans to have surgery
- had surgery on your face
- weakness of your forehead muscles, such as trouble raising your eyebrows
- drooping eyelids
- any other change in the way your face normally looks
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX 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** or **BOTOX 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 or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*® (rimabotulinumtoxinB) or *Dysport*® (abobotulinumtoxinA) 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

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take BOTOX® or BOTOX® Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles or skin.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.

What should I avoid while taking BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, or vision problems within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic**. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

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

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about BOTOX and BOTOX Cosmetic:
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for healthcare professionals. For more information about **BOTOX** and **BOTOX Cosmetic** call Allergan at 1-800-433-8871 or go to www.botox.com.

What are the ingredients in BOTOX and BOTOX Cosmetic?
Active ingredient: botulinum toxin type A
Inactive ingredients: human albumin and sodium chloride

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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

Myobloc® is a registered trademark of Solstice Neurosciences, Inc.
Dysport® is a registered trademark of Ipsen Biopharm Limited Company.

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