



MECHANISM OF ACTION

BOTOX[®] and BOTOX[®] Cosmetic contain a protein complex purified from the bacterium *Clostridium botulinum*. A component of this complex, Botulinum Toxin Type A is the important active ingredient. Type A is one of the seven distinct botulinum toxins produced by different strains of the bacterium. BOTOX[®] and BOTOX[®] Cosmetic decrease muscle activity by blocking overactive nerve impulses that trigger excessive muscle contractions or glandular activity. In addition, BOTOX[®] is believed to reduce neck pain associated with cervical dystonia through a temporary reduction in muscle activity and possibly through its influence on the pain sensory system (e.g., inhibiting the release of neurotransmitters involved in the transmission of painful sensations), although the exact mechanism of action is unknown.

Mechanism of Action

Phase I – Nerve-Muscle Communication is Blocked

BOTOX[®] and BOTOX[®] Cosmetic block the transmission of overactive nerve impulses to the targeted muscle by selectively preventing the release of the neurotransmitter acetylcholine (ACh) at the neuromuscular junction, temporarily preventing muscle contraction. This is primarily a local effect. BOTOX[®] may also prevent the release of pain-stimulating neuropeptides in peripheral nerves.

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 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).

IMPORTANT SAFETY INFORMATION

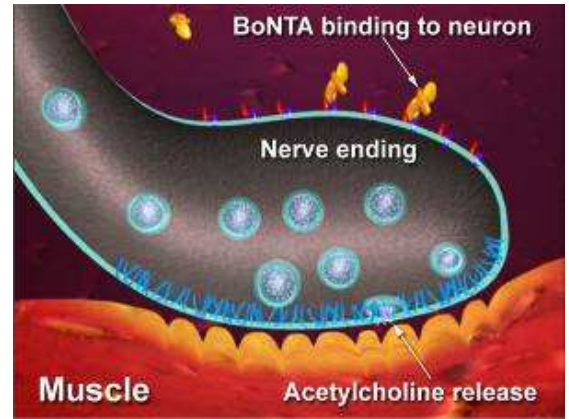
BOTOX[®] and BOTOX[®] Cosmetic may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX[®] or BOTOX[®] Cosmetic:

- **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.

Please see next page for additional Important Safety Information.

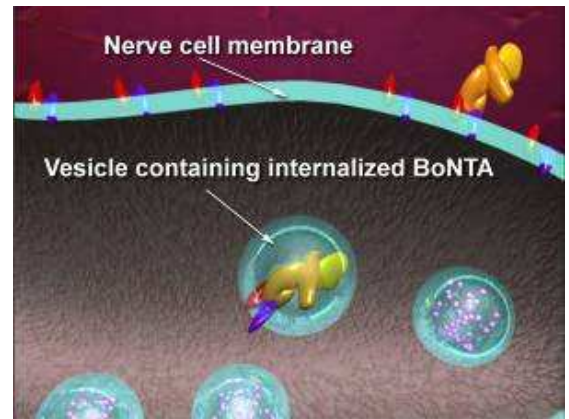
A) Binding:

The heavy chain portion of the active ingredient in BOTOX[®] (onabotulinumtoxinA) neurotoxin and BOTOX[®] Cosmetic (onabotulinumtoxinA) binds to the cell membrane of the motor nerve via an unidentified high-affinity “acceptor” molecule. This high-affinity binding action allows for efficient uptake of BOTOX[®] and BOTOX[®] Cosmetic by the motor nerve and facilitates selective, targeted treatment at the injection site.



B) Internalizing:

After binding, the BOTOX[®] and BOTOX[®] Cosmetic protein molecules pass through the cell membrane of the motor nerve and into its cytoplasm via a process called endocytosis. It is here that the enzymatic component (light chain) of the BOTOX[®] and BOTOX[®] Cosmetic protein molecule is activated.



IMPORTANT SAFETY INFORMATION (continued)

Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX[®] or BOTOX[®] Cosmetic:

- Swallowing problems may last for several months. 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" in Medication Guide.

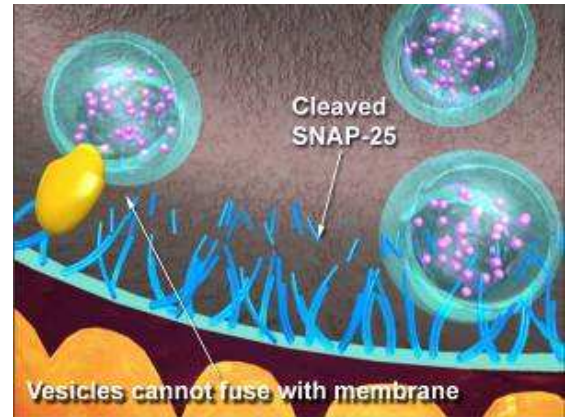
There has not been a confirmed serious case of spread of toxin effect away from the injection site when BOTOX[®] has been used at the recommended dose to treat severe underarm sweating, blepharospasm, or strabismus, or when BOTOX[®] Cosmetic (onabotulinumtoxinA) has been used at the recommended dose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

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).

Please see next page for additional Important Safety Information.

C) Blocking:

Inside the motor nerve, the light chain of the BOTOX[®] (onabotulinumtoxinA) and BOTOX[®] Cosmetic (onabotulinumtoxinA) protein molecule cleaves apart a protein (called SNAP25) that enables vesicles which store the neurotransmitter acetylcholine to attach to the cell membrane. Cleaving SNAP25 prevents these vesicles from fusing with the membrane and prevents the release of acetylcholine into the neuromuscular junction (the space between the motor nerve and the muscle). Thus, nerve impulses that control muscle contractions are blocked decreasing muscle activity.



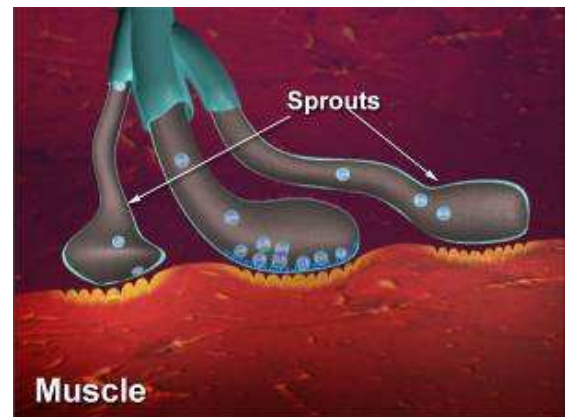
Cleaving SNAP25 also blocks release of neuropeptides involved in the transmission of painful sensations (including substance P, glutamate and calcitonin gene-related peptide, or CGRP), theoretically reducing pain sensitization of peripheral nerves. This may be how BOTOX[®] reduces the neck pain associated with cervical dystonia, although the exact mechanism of action is unknown.

Phase II – Nerve-Muscle Communication is Restored

The effect of BOTOX[®] and BOTOX[®] Cosmetic is generally temporary. Previous nerve impulse activity and associated muscle contractions resume over the course of a few to several months, depending on the individual patient and the indication for which they are being treated.

A) Nerve Sprouting:

New nerve endings sprout and connect to the muscle after the original nerve ending is blocked, renewing the ability of the nerve to cause muscle contractions.



IMPORTANT SAFETY INFORMATION (continued)

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

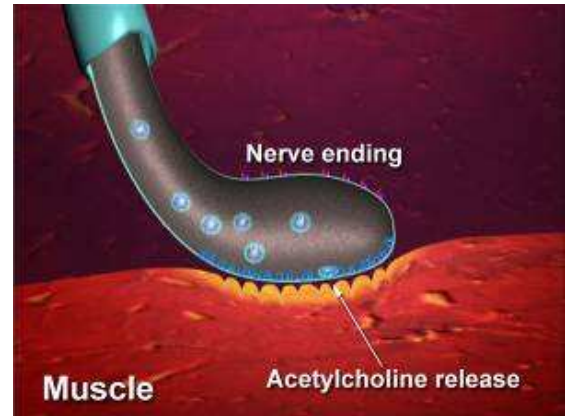
BOTOX[®] or BOTOX[®] Cosmetic can cause serious side effects. Other side effects of BOTOX[®] and BOTOX[®] Cosmetic include: dry mouth, discomfort or pain at the injection site,

tiredness, headache, neck pain, and eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes. Symptoms of an allergic reaction to BOTOX[®] and 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.

Please see next page for additional Important Safety Information.

B) Original Nerve Connection Re-established:

Eventually, the new nerve sprouts retract and the original nerve ending regains its function, suggesting that treatment with BOTOX[®] (onabotulinumtoxinA) neurotoxin and BOTOX[®] Cosmetic (onabotulinumtoxinA) does not permanently alter the neuromuscular junction.



IMPORTANT SAFETY INFORMATION (continued)

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.

For additional information refer to 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.

Please see the accompanying full Product Information, including Medication Guide, for BOTOX[®].

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