COVERAGE:

The use of botulinum toxin is considered **medically necessary** for the FDA-labeled indications of:

- Strabismus,
- Blepharospasm,
- Facial nerve (VII) disorders, or
- Cervical dystonia.

The use of botulinum toxin is considered a **medically necessary** off-label indication for the treatment of dystonia resulting in functional impairment (interference with joint function, mobility) and/or pain in patients with any of the following hereditary, degenerative, or demyelinating diseases of the central nervous system:

- Idiopathic torsion dystonia;
- Symptomatic torsion dystonia;
- Orofacial dyskinesia;
- Organic writer’s cramp;
- Hereditary spastic paraplegia;
- Neuromyelitis optica;
- Schilder’s disease;
- Spastic hemiplegia;
- Spasticity related to stroke;
- Infantile cerebral palsy;
- Spasmodic torticollis.

Other off label indications of botulinum toxin that are considered **medically necessary** include:

- laryngeal spasm and torticollis (whether congenital, due to childbirth injury, or traumatic);
- achalasia who have not responded to dilation therapy or who are considered poor surgical candidates; or
- treatment of chronic anal fissure.

Botulinum toxin is **considered medically necessary** when used for the treatment of primary hyperhidrosis or secondary gustatory hyperhidrosis in the small subset of patients with medical complications (i.e., skin maceration with secondary infections), or with significant functional impairment.

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Botulinum toxin is considered **NOT medically necessary** when used for the treatment of secondary hyperhidrosis as a substitute treatment of the underlying systemic disease process.

**NOTE:** For more information concerning botulinum toxin used as a treatment of hyperhidrosis see Medical Policy (MED201.014).

The use of botulinum toxin is considered **NOT medically necessary** as a treatment of wrinkles or other cosmetic indications.

The use of botulinum toxin is considered **experimental or investigational** for other indications, including but not limited to:

- headaches including migraine,
- tremors such as benign essential tremor,
- urinary incontinence due to bladder spasms (i.e. after spinal cord injuries),
- lower back pain,
- chronic motor tic disorder, and
- tics associated with Tourette syndrome.

**DESCRIPTION:**

Botulinum is a family of toxins produced by the anaerobic organism Clostridia botulinum. There are seven distinct serotypes designated as type A, B, C-1, D, E, F, and G. In this country, two preparations of botulinum are available and they are produced by two different strains of bacteria: type A (Botox) and type B (Myobloc). When administered intramuscularly, all botulinum toxins reduce muscle tone by interfering with the release of acetylcholine from nerve endings.

The U.S. Food and Drug Administration (FDA) - approved label for Botox states that it is indicated for:

- the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm, or
- VII nerve disorders in patients greater than 12 years old.

The FDA approved label for Myobloc states it is indicated for the treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain. Dystonia is a general term describing a state of abnormal or disordered tone of muscle (a state of continuous activity or tension beyond that related to the physical properties; i.e., it is active resistance to stretch). As an example, achalasia is a dystonia of the lower esophageal sphincter, while cervical dystonia
is also known as torticollis. Spasticity (a subset of dystonia),
describes a velocity-dependent increase in tonic-stretch reflexes with
exaggerated tendon jerks. Spasticity typically is associated with
injuries to the central nervous system. Spasticity is a common feature
of cerebral palsy.

Hyperhidrosis is excessive perspiration/sweating due to overactivity
of the sweat glands. The excessive sweating is beyond a level
required to maintain normal body temperature in response to heat
exposure, anxiety, or exercise. Primary hyperhidrosis usually occurs
in otherwise healthy persons. Secondary hyperhidrosis can result from
a variety of drugs or from underlying diseases/conditions or a genetic
disorder.

Gustatory hyperhidrosis (Frey's Syndrome) is unfavorable facial
sweating in response to hot or spicy foods.

Since its FDA approval in 1991, Botox has been used for a wide variety
of off-label indications. All these indications are associated with
dystonia, ranging from achalasia, spasticity after strokes, cerebral
palsy, and anal fissures. In addition to broadening indications, Botox
has also been used in children under 12 for the treatment of cerebral
palsy. It is anticipated that Myobloc will be used for the same range
of off label indications as Botox.

In April 2002, Botulinum Toxin Type A was approved by the FDA to be
marketed and labeled as Botox Cosmetic for use in the temporary
improvement of the appearance of moderate to severe glabellar facial
lines.

RATIONALE:

This policy is based on literature published since 1997. The
literature review focuses on randomized placebo-controlled clinical
trials. While the bulk of the literature is based on trials using
botulinum-A (i.e. Botox), it is anticipated that botulinum-B (Myobloc)
will be used for the same range of off label indications as botulinum-
A. There have been no comparisons of these two drugs, so their
relative efficacy is unknown. However, as part of the FDA approval
process, two randomized studies were performed using as control groups
either those with cervical dystonia who had an ongoing positive
response to botulinum-A or those whose initial good response to
botulinum-A had been secondarily lost. Patients in both trials
reported significant improvement, suggesting either of the drugs may
be used initially with a switch to the other drug if resistance
develops to the original drug used.
Achalasia

Achalasia is a neurogenic esophageal disorder of unknown origin characterized by impaired esophageal peristalsis and a lack of lower esophageal sphincter relaxation. While prior randomized controlled trials validated the efficacy of botulinum toxin in treating achalasia, until recently there was no randomized trial comparing botulinum toxin with pneumatic dilation (perhaps considered the gold standard non-surgical treatment.) In 1999, Vazzi and colleagues reported on a trial that randomized 42 patients with achalasia to receive either botulinum toxin or undergo pneumatic dilation. Pneumatic dilation resulted in a significantly higher cumulative remission rate. At 12 months, 70% of patients in the dilation group were still in remission compared to 32% of those in the botulinum toxin group. These results reflect the fact that the effects of botulinum toxin are known to be reversible and the fact that pneumatic dilation can provide durable treatment effects. The authors conclude that while botulinum toxin is an effective therapy, pneumatic dilation is the preferred medical treatment option.

Myofascial Pain Syndrome

Painful muscles (with increased tone and stiffness) containing trigger points characterize myofascial pain syndrome. Patients are often treated with injections of the trigger points with saline, dilute anesthetics, or dry needling. These trigger point injections, while considered established therapy, have been controversial since it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. Wheeler and colleagues conducted a randomized trial of 33 patients with myofascial pain syndrome who were randomized into 3 groups; one group receiving 50 units of botulinum toxin, one group receiving 100 units of botulinum toxin, and one group receiving normal saline. All 3 groups showed similarly significant treatment effects, based on the Neck Pain and Disability Visual Analogue Scale. When looking separately at the 9 patients who had two injections of botulinum compared to the 4 patients who had an injection of 100 units of botulinum following a placebo injection, the authors found improved pain relief in the group who had two injections. However, due to the small numbers who underwent a second injection, the difference was not clinically significant. The author suggests that further investigation using higher doses of botulinum and sequential injections are needed.

Spasticity Related to Stroke

Spasticity related to stroke may be a significant functional problem.
Plantar flexion spasticity may impede walking. Peripheral neurolysis with phenol injections has been used for many years as a form of treatment, but recently botulinum toxin injections have been investigated. Kirazli and colleagues compared the effects of phenol block and botulinum toxin in a randomized trial of 20 patients with spastic foot after stroke. The authors reported that both injections were associated with significant improvements, with botulinum toxin outperforming phenol injections after the first month of treatment (with equal treatment effects at 2 and 3 months). One possible advantage of the botulinum toxin is the relative ease of the procedure (15 to 30 minutes), while phenol injection may take up to 2 hours to target a motor nerve for injection. Smith and colleagues investigated the use of botulinum toxin in a trial that randomized 21 patients with upper limb spasticity related to stroke or head injury. There was a significant reduction in spasticity in the wrist and fingers in the botulinum group. The effects were transitory and disappeared at 12 weeks.

**Anal Fissure**

Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter and is treated surgically with an internal sphincterotomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin represented a logical medical approach. Maria and colleagues reported on a study that randomized 30 patients with chronic anal fissure to receive either 2 injections of 20 units of botulinum toxin (on either side of the fissure) or 2 injections of saline. After 2 months, 11 patients in the treatment group reported healing, compared to only 2 in the control group. The 4 patients who still had fissures after 2 months, underwent retreatment with botulinum toxin; 2 of these 4 patients reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80%. Nitroglycerin ointment has also been used to successfully treat anal fissure. Recently Brisinda and colleagues compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group.

**Tremor**

Tremor may be defined as alternate or synchronous contractions of antagonistic muscles. Some patients may be disabled by severe or task-specific tremors. Tremors are also a frequent component of dystonias. Successful treatment of dystonias results in an improvement in tremors. Botulinum toxin has been investigated in patients with
tremors unrelated to dystonias. One randomized study involved 10 patients with essential head tremor. The patients were randomized to receive botulinum injections into the sternocleidomastoid and splenius capitus muscle or were in the control group (non-treatment). Five patients improved in the treatment group compared to 3 in the control group. The lack of statistical significance may be related to the small size of the study.

**Migraine**

The interest in using botulinum as a treatment of migraine stemmed from the observation that patients receiving pericranial injections of botulinum toxin for other reasons reported a decrease in the incidence of migraine. While it may exert its effect by relieving the associated muscle tension associated with migraine, others have proposed it is due to an independent action. Silberstein and colleagues reported on a double blind, randomized, placebo controlled trial of pericranial injections of botulinum toxin as a prophylactic treatment of migraine. A total of 123 patients were randomized to receive either placebo injections or 25U (or 75U) of botulinum toxin injected in various sites pericranially. The patients were followed for 3 months after the injections, during which time they kept a headache diary. A significantly greater proportion of patients receiving 25 U of botulinum reported a decrease of two or more migraines. While this study suggests that botulinum toxin may be an effective prophylactic therapy for migraines, there is no underlying scientific explanation for the treatment effect. The lack of a dose response effect also undermines the findings. Additionally there is no data comparing botulinum to other prophylactic therapies, such as calcium channel blockers, beta blockers, non-steroidal anti-inflammatory drugs, or selective serotonin reuptake inhibitors.

**Tension Headache**

Rollnik and colleagues reported on a double blind placebo controlled trial of botulinum A toxin in the treatment of tension headache. The study included 21 subjects who were randomized to receive either pericranial injections of botulinum A or a placebo. Evaluations at 4, 8 and 12 weeks resulted in no significant difference in outcome between the treatment and placebo group. Another randomized trial of 37 patients with tension headaches reported that botulinum treatment was associated with an improvement in headache intensity. However, at baseline, the number of headache free days was greater in the group randomized to receive botulinum treatment (which limited interpretation).
Cervicogenic Headache

Freund and colleagues reported on a placebo controlled trial that randomized 26 patients with chronic headache (related to whiplash injury) to receive either botulinum toxin or placebo injections. The treatment group reported a significant improvement in pain while the placebo group reported no improvement. The study design was flawed in that at baseline less pain was reported by the placebo group.

Hyperhidrosis

Botulinum toxin is a potent neurotoxin that blocks cholinergic nerve terminals (symptoms of botulism include cessation of sweating). Therefore intracutaneous injections have been investigated as a treatment of gustatory hyperhidrosis and primary hyperhidrosis.

Other Reported Indications without Randomized Controlled Trials

Several small case series have reported promising results when Botulinum Toxin is used for patients with excessive drooling (which may be associated with Parkinson disease). Refractory headaches (which may be associated with chronic daily headaches or migraines) may also be associated with increased muscle tension of the pericranial muscles. Wheeler reported on a case series of 4 patients with daily headaches and identifiable areas of increased muscle tension treated with Botulinum Toxin. The author reported that the patients reported decreased frequency and severity of headaches. This finding should be confirmed by larger controlled studies.

PRICING:

Electromyographic (EMG) guidance may be used to direct the injection of the botulinum toxin, particularly if the larynx or esophagus is being treated. If so, EMG guidance is considered an integral part of the procedure and no additional reimbursement for the EMG is warranted.

Injection of the vocal cords is done in association with laryngoscopic guidance. The laryngoscope is considered an integral part of the procedure and separate billing for the laryngoscope and injection is not warranted.

Botulinum toxin as a treatment of achalasia requires a separate endoscopy procedure, which is billed separately.

REFERENCES:


• Schnider, P., et al. "Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms." British Journal...
• "Botulinum Toxin" BCBSA TEC Assessment Program (1996); Tab 6; 5.01.05.

DISCLAIMER:

State and federal law, as well as contract language, including definitions and specific inclusions/exclusions, takes precedence over Medical Policy and must be considered first in determining coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Any benefits are subject to the payment of premiums for the date on which services are rendered. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.
HMO Blue Texas physicians who are contracted/affiliated with a capitated IPA/medical group must contact the IPA/medical group for information regarding HMO claims/reimbursement information and other general polices and procedures.