POLICY:  Botulinum Toxins – Botox® (onabotulinumtoxinA for injection – Allergan)

APPROVAL DATE:  05/08/2019

OVERVIEW

Botox® (onabotulinumtoxinA), is indicated for the following:

- blepharospasm associated with dystonia, including benign essential blepharospasm or seventh nerve disorders, and strabismus in patients ≥ 12 years of age;
- cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia;
- hyperhidrosis, primary axillary, that is inadequately treated with topical agents;
- migraine headache prophylaxis in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours per day or longer);
- overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have inadequate response to or are intolerant of an anticholinergic medication;
- spasticity, lower limb, in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors;
- spasticity, upper limb, in adult patients to decrease the severity of increased muscle tone in elbow flexors, wrist flexors, finger flexors, and thumb flexors; AND
- urinary incontinence due to detrusor overactivity associated with a neurological condition (e.g., spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.¹

In addition, botulinum toxin type A has been used to treat a multitude of disorders characterized by abnormal muscle contraction.² The benefit of this drug has also been demonstrated in the treatment of gastrointestinal, genitourinary, ocular, and autonomic nervous system disorders.²,³

Botox® Cosmetic (onabotulinumtoxinA) is indicated for the temporary improvement in appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adult patients, moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients, and moderate to severe forehead lines associated with frontalis muscle activity.⁴ Botox Cosmetic is not included in this policy.

Toxin distribution varies between the commercially available botulinum toxin A products, Botox and Dysport® (abobotulinumtoxinA), and Xeomin® (incobotulinumtoxinA).¹,⁶,⁷ It has been postulated that differences in albumin concentration control diffusion of toxin from the injection site (Botox contains 500 mcg of albumin, while Dysport contains 125 mcg of albumin and Xeomin contains 1 mg of albumin). This concept has been supported by animal studies revealing a higher safety margin for intramuscularly injected Botox than Dysport. In addition, the labels for the botulinum toxin type A products (Botox, Dysport, and Xeomin) state that there is a lack of interchangeability between the products for various reasons, including differences in the units of biological activity.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Botox. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for 1 year in duration. In cases where a dosing interval is provided in months, one month is equal to 30 days. Previous therapy is required to be verified by a clinician when noted in the criteria as [verification of therapies required].
Medical benefit coverage is not recommended for Botox Cosmetic.

**RECOMMENDED AUTHORIZATION CRITERIA**

**FDA-Approved Indications**

1. **Blepharospasm Associated with Dystonia or Strabismus.** Approve for 1 year.

   **Dosing.** Approve the following dosing regimens (A or B):
   
   A) **For blepharospasm:** Approve up to a maximum dose of 200 units, administered not more frequently than once every 3 months.
   
   B) **For strabismus:** Approve up to a maximum dose of 25 units in any one muscle, administered not more frequently than once every 3 months.

   Botox prescribing information states that treatments may be repeated once every 3 months for blepharospasm. A cumulative maximum dose for this indication should not exceed 200 units in any 30-day interval. There appears to be little benefit in injecting more than 5 units per site.

2. **Cervical Dystonia (torticollis).** Approve for 1 year.

   (Note: Cervical dystonia is also known as spasmodic or cervical torticollis).

   **Dosing.** Approve up to a maximum dose of 300 units, administered not more frequently than once every 3 months.

3. **Hyperhidrosis, Primary Axillary.** Approve for 1 year if the patient has tried at least one topical agent (e.g., topical aluminum chloride, Qbrexza™ [glycopyrronium cloth 2.4% for topical use]).

   **Dosing.** Approve up to a maximum dose of 50 units per axilla, administered not more frequently than once every 3 months.

   Topical antiperspirants (e.g., topical aluminum chloride) or Qbrexza are the recommended first-line therapy for the treatment of primary axillary hyperhidrosis. In general, Botox is not recommended to be injected more frequently than once every 3 months, and botulinum toxins appear to have an approximately 3-month duration of effect or longer, depending on the site of injection.

4. **Migraine Headache Prophylaxis in Patients with Chronic Migraine.** Approve for 1 year in patients who meet all of the following conditions (A, B, C, and D):

   A) Patient has ≥ 15 migraine headache days per month with headache lasting 4 hours per day or longer (prior to initiation of Botox therapy); AND

   B) Patient has tried at least two other prophylactic pharmacologic therapies, each from a different pharmacologic class (e.g., β-blocker, anticonvulsant, tricyclic antidepressant) [verification of therapies required]; AND

   C) Patient meets ONE of the following (i or ii):

   i. Patient has tried at least one triptan therapy (e.g., almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan); OR

   ii. Patient has a contraindication to triptan(s) according to the prescribing physician; AND
D) Botox is being prescribed by or after consultation with a neurologist or headache specialist.

Dosing. Approve up to a maximum dose of 155 units, administered not more frequently than once every 12 weeks.

5. Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency. Approve for 1 year if the patient has tried at least one other pharmacologic therapy (e.g., Myrbetriq® or an anticholinergic medication [for example: oxybutynin, tolterodine tartrate, trospium chloride, Enablex®, Toviaz®, Vesicare®]).

(Note: For treatment of urinary incontinence associated with a neurological condition [e.g., spinal cord injury, multiple sclerosis], see FDA-Approved Indications criterion #8 [below].)

Dosing. Approve up to a maximum dose of 100 units, administered not more frequently than once every 12 weeks.

Use of oral antimuscarinic agents or oral β3-adrenoceptor agonists is the first-line pharmacologic treatment of non-neurogenic overactive bladder/detrusor hyperreflexia. The use of Botox for non-neurogenic overactive bladder in children (n = 21) who are resistant to common treatments has been shown to be a safe and effective treatment.


(Note: For other forms of spasticity that do not fit this condition of approval, see Other Uses with Supportive Evidence, Spasticity).

Dosing. Approve up to a maximum dose of 400 units (divided among 5 muscles), administered not more frequently than once every 12 weeks.

7. Spasticity, Upper Limb. Approve for 1 year.

(Note: For other forms of spasticity that do not fit this condition of approval, see Other Uses with Supportive Evidence, Spasticity).

Dosing. Approve up to a maximum dose of 400 units divided among selected muscles, administered not more frequently than once every 12 weeks.

8. Urinary Incontinence Associated with a Neurological Condition (e.g., spinal cord injury, multiple sclerosis). Approve for 1 year if the patient has tried at least one other pharmacologic therapy (e.g., Myrbetriq or an anticholinergic medication [for example: oxybutynin, tolterodine tartrate, trospium chloride, Enablex, Toviaz, Vesicare]).

(Note: For treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, see FDA-Approved Indications criterion #5 [above].)

Dosing. Approve up to a maximum dose of 200 units, administered not more frequently than once every 12 weeks.

Other Uses with Supportive Evidence
9. **Achalasia.** Approve for 1 year.

**Dosing.** Approve up to a maximum dose of 100 units into the lower esophageal sphincter, administered not more frequently than once every 3 months.

The clinical data on the use of botulinum toxin A for treatment of achalasia are extensive and suggest that it is effective in the majority of patients treated; 70% to 100% of patients experience short-term symptomatic relief. A large amount of data from both uncontrolled studies and randomized, controlled studies support the effectiveness of botulinum toxin A as a non-invasive therapeutic alternative. The American College of Gastroenterology (ACG) clinical guideline for the diagnosis and management of achalasia (2013) recommends the use of botulinum toxin therapy in patients who are not good candidates for more definitive therapy with pneumatic dilation or surgery (myotomy).

Of note, Botox has been studied for achalasia in several trials. Doses of 80 to 100 units of Botox were commonly used. Doses higher than 100 units of Botox per treatment have not been shown to be more effective. In general, Botox is not recommended to be injected more frequently than once every 3 months, and botulinum toxins appear to have an approximately 3-month duration of effect or longer, depending on the site of injection.

10. **Anal Fissures (anal sphincter).** Approve for 1 year.

**Dosing.** Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

There is an extensive amount of data from open-label studies; randomized, placebo-controlled trials; and randomized, comparative trials supporting the efficacy of botulinum toxin A in the treatment of anal fissures. The majority of the available data are evaluating use of Botox. Overall, injections of botulinum toxin A have resulted in healing of 60% to 80% of anal fissures. Botulinum toxin A appears to be a safe and effective short-term treatment of chronic anal fissure, demonstrating a healing rate of 70% to 98% after 2 to 4 months. Botox has been shown to be more effective than topical nitroglycerin but less effective than surgery in inducing and maintaining fissure healing. The ACG clinical guideline for the management of benign anorectal disorders (2014) recommends the use of botulinum toxin therapy or surgical internal anal sphincterotomy in patients who do not respond to conservative or topical pharmacologic agents, such as a calcium channel blockers or nitrates.

Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval. Of note, there is not a consensus on dosage for this indication, and higher doses may improve healing and are as safe as lower doses. A wide range of doses have been used in previous trials for anal fissures, ranging from 5 units to 100 units of Botox.

11. **Benign Prostatic Hyperplasia (BPH).** Approve for 1 year if the patient has tried at least two other therapies (e.g., anticholinergic agent, alpha1-blocker, 5 alpha-reductase inhibitor, transurethral resection of the prostate [TURP], transurethral microwave thermotherapy [TUMT], transurethral needle ablation [TUNA®], various forms of surgery).

**Dosing.** Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.
According to the American Urological Association (AUA) guidelines on the treatment of BPH, botulinum toxin should be considered only after insufficient improvement on other pharmacotherapy. In one 12-month, randomized, double-blind, placebo-controlled study in 30 men with moderate to severe symptoms of urinary obstruction as a result of BPH, Botox significantly decreased symptom scores, prostate-specific antigen (PSA) concentrations, prostate volume, and post-void residual urine volume from baseline compared with placebo. Significantly more patients treated with Botox reported subjective symptomatic relief compared with those treated with placebo. This study did not specify previously tried therapies. Similar results were seen in a prospective, single-armed cohort study in 64 men diagnosed with lower urinary tract symptoms due to BPH with unsatisfactory response to combined alpha1-blocker and 5 alpha-reductase inhibitor therapy for ≥6 months. In another study involving 41 men with symptomatic BPH refractory to medical treatment, 75.6% of patients experienced ≥30% improvement in lower urinary tract symptom and quality-of-life indices. Other small studies show improvement after 1 month of the transperineal or intraprostatic Botox injection with sustained treatment response for 6 to 8 months.

Of note, doses ranging from 100 to 600 units of Botox have been used for this indication. Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.

12. **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction.** Approve for 1 year.

**Dosing.** Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Data from several open-label studies, as well as one randomized, placebo-controlled trial, support the efficacy of Botox in the treatment of chronic facial pain/chronic facial pain associated with hyperactivity of the masticatory muscles.

Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.

An average of 35 units of Botox bilaterally were used in one study. In another trial, 50 units of Botox were injected into each masseter, and 25 units of Botox were injected into each temporalis muscle.

13. **Chronic Low Back Pain (CLBP).** Approve for 1 year in patients who meet the following conditions (A and B):

A) Patient has tried at least two other pharmacologic therapies (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], antispasmodics, muscle relaxants, opioids, antidepressants); AND

B) Botox is being used as part of a multimodal therapeutic pain management program.

**Dosing.** Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

In one 8-week, randomized, double-blind, placebo-controlled trial in 31 patients with CLBP (no causative factor identified in the majority of patients; history of disc disease in 6 patients, discectomy in 3 patients, and trauma in 4 patients), Botox in addition to their current pharmacologic treatment regimen resulted in significantly greater improvement in pain relief and degree of disability compared with placebo. Short-term retrospective studies also suggest benefit from this form of treatment in CLBP. A 14-month, open-label, prospective study evaluated the short- and long-term effects of
paraspinal muscle injections of Botox in 75 patients with refractory CLBP. A total of 53% and 52% of patients reported significant pain relief at 3 weeks and 2 months, respectively.

Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\(^1\)

### 14. Dystonia, other than cervical (e.g., focal dystonias, tardive dystonia, anismus).
Approve for 1 year. (Note: For cervical dystonia, see FDA-Approved Indications criterion #2 [above]).

**Dosing.**\(^1\) Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

In one large, prospective, 5-year, open-label study in 477 patients with various focal dystonias (symptomatic despite optimum pharmacological or surgical therapy), 93% of patients reported moderate to marked relief of their spasm after treatment with Botox.\(^30\) Data from several other smaller open-label studies, case reports, and small, randomized, controlled trials further support the effectiveness of Botox in the treatment of non-cervical dystonias.\(^31-35,74\) Guidelines from the American Academy of Neurology (AAN) support use of botulinum toxins in focal dystonias of the upper extremity (should be considered; Level B recommendation).\(^75\)

Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\(^1\)

**Duration of therapy.** Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).

NOTE TO NURSE CLINICIAN: Approval duration should align with dose management criteria (for example, if multiple doses are approved, the duration of the authorization should be aligned with the interval necessary to complete the approved number of doses). The maximum duration of each approval is 1 year.

### 15. Essential Tremor (ET).
Approve for 1 year if the patient has tried at least one other pharmacologic therapy (e.g., primidone, propranolol, benzodiazepines, gabapentin, topiramate).

**Dosing.**\(^1\) Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

According to the clinical practice parameter on essential tremor (ET) by the American Academy of Neurology, propranolol and primidone are first-line therapy in the treatment of essential tremor.\(^85\) Second-line medication options include alprazolam, atenolol, (monotherapy), sotalol, gabapentin, and topiramate. Botulinum toxin A may also reduce tremor. The guidelines recommend that botulinum toxin A may be considered in medically refractory cases of limb, head, and voice tremor associated with ET (Level C for limb, head, and voice tremor). Botox was shown to significantly improve tremor severity and postural tremor outcomes compared with placebo in two randomized, double-blind, placebo-controlled studies in a total of 158 patients with moderate to severe essential hand tremor.\(^86,87\) Open-label studies as well as one double-blind, placebo-controlled study support the effectiveness of botulinum toxin A in improving essential voice tremor and essential head tremor (head tremor without dystonia).\(^88-90\)
Definitive dosing is not established and may vary by tremor location.\textsuperscript{2,86-90,96,97} In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\textsuperscript{1}

16. **Frey’s Syndrome (gustatory sweating).** Approve for 1 year.

**Dosing.\textsuperscript{1}** Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Botulinum toxin A has been shown to be highly effective in treating the symptoms (i.e., hyperhidrosis and facial flushing) of Frey’s syndrome and has emerged as the treatment of choice in the treatment of this condition.\textsuperscript{11,43,44} In six open-label trials in a total of 132 patients with Frey’s syndrome/gustatory sweating, injections of Botox resulted in the complete absence or pronounced improvement of symptoms in all patients studied.\textsuperscript{43-49} Although AAN guidelines only state that botulinum toxin “may be considered” for this use (Level C), Botox is recommended as a first-line option for Frey’s syndrome by the International Hyperhidrosis Society.\textsuperscript{24,76}

Of note, doses can widely vary based on patient factors such as extent of skin surface involvement; in one review, doses ranged from 2.5 to 100 units of Botox, with an average of 31.3 units per dose.\textsuperscript{44} Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\textsuperscript{1}

17. **Hyperhidrosis, Palmar/Plantar and Facial.** Approve for 1 year if the patient has tried at least one topical agent (e.g., aluminum chloride).

**Dosing.\textsuperscript{1}** Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Overall, topical antiperspirants (e.g., aluminum chloride) are the recommended first-line therapy for the treatment of primary focal hyperhidrosis; other conventional treatments include oral anticholinergics.\textsuperscript{8-10,15} Topical treatment is more effective in mild cases compared with more severe cases.\textsuperscript{11} The efficacy of Botox is well-established in the treatment of primary focal/palmar hyperhidrosis based on data from both randomized, double-blind, placebo-controlled studies and open-label studies.\textsuperscript{3,11,15} Guidelines from the International Hyperhidrosis Society support use of Botox in patients who have failed to respond to topical therapy.\textsuperscript{22-24} AAN guidelines state that botulinum toxins are probably safe and effective and should be considered for palmar hyperhidrosis (plantar and facial hyperhidrosis are not addressed in the AAN guideline).\textsuperscript{76}

Of note, dosing varies by patient and by site of hyperhidrosis. Typical doses for the palms and soles are 100 units of Botox but can reach 150 to 200 units depending on patient size.\textsuperscript{49} Dosing of Botox for facial hyperhidrosis can range from 50 to 100 units total, but injection into the facial muscles is complex and varies widely by individual patient.\textsuperscript{8} Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\textsuperscript{1}

18. **Myofascial Pain.** Approve for 1 year.
Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Data from several retrospective reviews and open-label trials support the efficacy of Botox in the treatment of myofascial pain syndromes associated with various muscle groups. In one randomized, controlled trial in 40 patients with chronic myofascial pain of various forms, Botox resulted in a significantly greater reduction in pain score from baseline compared with intramuscularly administered methylprednisolone at 30 days and 60 days post injection. Another double-blind, randomized, placebo-controlled study involving 30 patients showed no difference in spontaneous and evoked pain reduction between Botox and isotonic saline injection recipients.

Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.

19. Ophthalmic Disorders, Other Than Blepharospasm or Strabismus (e.g., esotropia, exotropia, nystagmus, facial nerve paresis). Approve for 1 year.

(Note: For blepharospasm associated with dystonia or strabismus, see FDA-Approved Indications criterion #1 [above]).

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Botulinum toxin A has been successful in improving or treating many ophthalmic disorders. One retrospective review (n = 54) concluded that Botox may have a role in the treatment of esotropia in patients > 18 months of age. Botox improved visual acuity in one small, open-label study in patients with acquired symptomatic nystagmus from multiple sclerosis or brain-stem hemorrhage as well as in case reports. Data from uncontrolled studies have shown Botox to be beneficial in the treatment of sixth nerve palsy.

20. Plantar Fasciitis. Approve for 1 year if the patient has tried two other treatment modalities (e.g., padding and strapping of the foot, therapeutic orthotic insoles, oral anti-inflammatory drugs, corticosteroid injections, stretching).

Dosing. Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

In one randomized, double-blind study (n = 36), botulinum toxin A exhibited more rapid and sustained improvement over the duration of the study as compared with the patients who received steroid injections. The clinical consensus statement on the diagnosis and treatment of heel pain (developed by the American College of Foot and Ankle Surgeons) published in 2010, botulinum toxin injection is listed as a Tier 2 option (Grade I); Tier 1 treatment options include: padding and strapping of the foot (Grade B), therapeutic orthotic insoles (Grade B), oral anti-inflammatory agents (Grade I), corticosteroid injections (Grade B), and achilles and plantar fascia stretching (Grade B) [Grade B recommendations are supported by fair evidence, Grade I recommendations indicate there is insufficient evidence to make a recommendation].

05/08/2019
Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\(^1\) Of note, a dose of 250 units of botulinum toxin A was cited in the above study (botulinum product not specified), divided among the calf muscles and soleus.\(^91\)

### 21. Salivary Hypersecretion

**Approve for 1 year.**

**Dosing.**\(^7\) Approve up to a maximum dose of 100 units (50 units per side), administered not more frequently than once every 16 weeks.

Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson’s Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amyotrophic lateral sclerosis (ALS).\(^3\) Most of the data comes from open-label studies with small groups of patients (using Botox or Dysport). Overall, up to two-thirds of patients in these studies experienced moderate or marked improvement. A review of the literature on medical treatment of sialorrhea found that Botox is probably effective for the treatment of this condition (level B evidence).\(^80\) AAN guidelines note that botulinum toxin is probably safe and effective and should be considered (Level B).\(^76\)

A wide variety of doses have been studied.\(^64\) Some studies have used weight-based dosing of Botox and others have used fixed doses. One fixed dose studied was 50 units of Botox per parotid gland. Definitive dosing is not established. Of note, Xeomin is indicated for this use at a dose of 100 units (50 units per side), administered not more frequently than once every 16 weeks.\(^7\) Recommendations for maximum dosing and frequency for Botox are based on suggested relative conversion of 1:1 for Botox to Xeomin.\(^93\)

### 22. Spasticity, Other Than Lower and Upper Limb (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm)

**Approve for 1 year.**

*(Note: For lower and upper limb spasticity, see FDA-Approved Indications criteria #6 and #7 [above]).*

**Dosing.**\(^1\) Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Botulinum toxin is the most widely used treatment for focal spasticity.\(^61\) Neurosurgery and oral medications have a long history in spasticity treatment (e.g., baclofen, benzodiazepines, phenytoin, or gabapentin), yet they have dose-limiting side effects and limited diffusion across the blood brain barrier.\(^40\) Several randomized, double-blind, placebo-controlled trials support the effectiveness of botulinum toxin A in the treatment of focal spasticity/focal hypertonia.\(^26,63-67\) For lower limb spasticity, four randomized controlled trials in more than 100 patients treated with botulinum toxin A had significant improvement in Ashworth scores or improved muscle tone.\(^62\) In both upper and lower limb spasticity, studies have shown modest improvement of active limb function in a select subgroup of patients. Other randomized, controlled trials evaluated botulinum toxin A for the management of upper limb spasticity in children with cerebral palsy and showed significant improvement in spasticity/tone, range of motion, and functional gains after botulinum toxin A injections.\(^68\) The majority of the data evaluated the use of Botox. Treatment with botulinum toxin A in hemifacial spasm appears to remain effective over long-term use of several years (4 to 10 years); most cases do not require a dosage increase.\(^69\) In an observational study, patients (n = 133) with hemifacial spasm or reinnervation synkinesias were exclusively treated with either Botox or Dysport for 6 years (range, 2 to 12 years)
Botulinum Toxins - Botox

Page 10

with a minimum of eight consecutive treatments.\textsuperscript{70} The therapeutic effect was stable throughout observation in 85\% of patients. There were no differences between both drugs with respect to efficacy or safety. Per the AAN, botulinum toxin is established effective in upper and lower limb spasticity and in cerebral palsy (Level A), and it may be considered in hemifacial spasm (Level C).\textsuperscript{75,77}

Of note, a wide variety of doses may be appropriate depending on the etiology and site of spasticity. Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\textsuperscript{1}

\textbf{23. Speech/Voice Disorder (e.g., dysphonias).} Approve for 1 year.

\textbf{Dosing.}\textsuperscript{1} Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Botulinum toxin A is the most widely accepted treatment for spasmodic dysphonia, a focal laryngeal dystonia, viewed as the treatment of choice by the American Academy of Otolaryngology-Head and Neck Surgery.\textsuperscript{36} Per the guideline, clinicians should offer, or refer to a clinician who can offer, botulinum toxin injections for treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia. Several prospective, open-label studies support the effectiveness of Botox in improving tracheoesophageal speech failure, ventricular dysphonia, and voice tremor.\textsuperscript{28,40-42} AAN guidelines note that botulinum toxin is probably effective and should be considered for adductor type laryngeal dystonia (Level B).\textsuperscript{75}

Of note, doses vary depending on the etiology of the speech/voice disorder. For example, in spastic dysphonia, 1.25 to 5 units of Botox have been injected into each affected muscle, with doses up to 25 units.\textsuperscript{2} Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.\textsuperscript{1}

\textbf{24. Tinnitus.} Approve for 1 year in patients who meet all of the following conditions (A, B, and C):

A) Patient has tried at least two other pharmacologic therapies (e.g., lidocaine, antihistamines, antidepressants, anxiolytics, diuretics, anticonvulsants, antispastics); AND

B) Patient has tried tinnitus retraining therapy; AND

C) Botox is being prescribed by an ear/nose/throat (ENT) physician (i.e., otolaryngologist – head and neck surgery).

\textbf{Dosing.}\textsuperscript{1} Approve up to a maximum dose of 400 units, administered not more frequently than once every 3 months.

Currently available oral agents have been tried with variable results and have been limited in their ability to successfully control tinnitus long-term. Tinnitus retraining therapy may be considered the most successful treatment available to date.\textsuperscript{39} In one 4-month, randomized, double-blind, placebo-controlled study in 30 patients with tinnitus, Botox doses ranging from 20 to 50 units resulted in significant subjective improvement in seven patients compared with placebo and a significant decrease in tinnitus handicap inventory scores compared with baseline. Clinical practice guidelines from the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF) on the diagnosis and management of tinnitus do not mention the use of botulinum toxin for the treatment of tinnitus.\textsuperscript{38}
Definitive dosing is not established. In general, the Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.¹

**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Botox has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. *(Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)*

1. **Cosmetic Uses** (e.g., facial rhytides, frown lines, glabellar wrinkling, horizontal neck rhytides, mid and lower face and neck rejuvenation, platysmal bands, rejuvenation of the periorbital region). Cosmetic use is not recommended for coverage as this indication is excluded from coverage in a typical medical benefit.

2. **Fibromyalgia.** More data are needed to define the place in therapy of Botox in the treatment of fibromyalgia. A small pilot study involving 16 patients concluded botulinum toxin A injections into fibromyalgia trigger points offered more relief (up to 16 weeks minimum) compared with local saline or anesthetic injections; it was concluded Botox is effective in the treatment of fibromyalgia.³⁷ Other small studies have shown effectiveness of Botox in pain relief post injection.² Botox is not mentioned in guidelines for the treatment of fibromyalgia.

3. **Gastroparesis.** The ACG issued clinical guidelines on the management of gastroparesis (2013).¹⁶ ACG does not recommend the use of botulinum toxin injected into the pylorus as a treatment for gastroparesis. This is based on two double-blind, placebo-controlled studies which did show some improvement in gastric emptying, but no improvement in symptoms compared with placebo.

4. **Vaginismus.** More data are needed to define the place in therapy of Botox in the treatment of vaginismus. The use of Botox for the treatment of vaginismus has been evaluated in a few small studies with successful outcomes.²⁵

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**REFERENCES**

Botulinum Toxins - Botox


05/08/2019
Botulinum Toxins - Botox

Botulinum Toxins - Botox

OTHER REFERENCES UTILIZED

HISTORY

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy</td>
<td>--</td>
</tr>
<tr>
<td>Selected revision</td>
<td>Migraine prophylaxis: Added requirement to verify prior prophylactic therapies; examples of triptans added to triptan criterion.</td>
</tr>
<tr>
<td>Selected revision</td>
<td>Dosing updated throughout policy to simplify maximum approved dosing regimens.</td>
</tr>
<tr>
<td>Early annual revision</td>
<td><strong>Cervical Dystonia (torticollis):</strong> Clarification noted that cervical dystonia may also be called spasmodic torticollis or cervical torticollis. <strong>Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency:</strong> Clarification noted to refer to approval condition #8 for urinary incontinence associated with a neurological condition. <strong>Urinary Incontinence Associated with a Neurological Condition:</strong> Clarification noted to refer to approval condition #5 for overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>8/01/2018</td>
</tr>
<tr>
<td>8/22/2018</td>
</tr>
<tr>
<td>12/05/2018</td>
</tr>
<tr>
<td>05/08/2019</td>
</tr>
</tbody>
</table>