

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

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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 adults 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;
- lower limb spasticity in adults to decrease the severity of increased muscle tone in ankle and toe flexors;
- lower limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy;
- upper limb spasticity in adults to decrease the severity of increased muscle tone in elbow flexors, wrist flexors, finger flexors, and thumb flexors;
- upper limb spasticity in pediatric patients 2 to 17 years of age; 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 adults, moderate to severe lateral canthal lines associated with orbicularis oculi activity in adults, and moderate to severe forehead lines associated with frontalis muscle activity.⁴ Botox Cosmetic is not included in this policy.

Studies have attempted to establish a conversion ratio between botulinum toxin products, with variable results. In general, conversion ratios of 1:1 for Botox to Xeomin® (incobotulinumtoxinA), 1:3 for Botox to Dysport® (abobotulinumtoxinA), and 1:50 to 1:100 for Botox to Myobloc® (rimabotulinumtoxinB) have been suggested.^{5,6}

Other Uses with Supportive Evidence

Botox has been studied in a variety of indications outside of FDA-approved uses. Literature is available to support use of Botox in the following conditions:

- **Achalasia:** 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.^{7,8} 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.⁹⁻¹¹ The American College of Gastroenterology (ACG) clinical
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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).¹²

- **Anal Fissures:** 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.^{7,13-15} 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.¹⁶ 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.¹⁷ 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.¹⁴
- **Chronic Facial Pain/Pain Associated with Temporomandibular Dysfunction:** 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.¹⁸⁻²¹
- **Chronic Low Back Pain (CLBP):** 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.²² 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.²³
- **Dystonia, other than cervical (e.g., focal dystonias, tardive dystonia, anismus, laryngeal dystonia/spasmodic dysphonia):** 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.²⁴ 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.²⁵⁻³⁰ 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).³¹ 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.³² 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. AAN guidelines note that botulinum toxin is probably effective and should be considered for adductor type laryngeal dystonia (Level B).³¹
- **Essential Tremor:** 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.³³ 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.^{34,35} 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).³⁶⁻³⁸

- **Frey’s Syndrome (gustatory sweating):** 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.³⁹⁻⁴¹ 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.⁴⁰⁻⁴⁶ 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.^{47,48}
- **Hyperhidrosis, Palmar/Plantar and Facial:** 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.^{8,49-51} Topical treatment is more effective in mild cases compared with more severe cases.³⁹ 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.^{3,8,39} Guidelines from the International Hyperhidrosis Society support use of Botox in patients who have failed to respond to topical therapy.^{47,52,53} 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).⁴⁸
- **Myofascial Pain:** 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.^{18,54} 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.⁵⁵ 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.⁵⁶
- **Ophthalmic Disorders, Other Than Blepharospasm or Strabismus (e.g., esotropia, exotropia, nystagmus, facial nerve paresis):** 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.⁵⁷ 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.^{58,59} Data from uncontrolled studies have shown Botox to be beneficial in the treatment of sixth nerve palsy.^{60,61}
- **Plantar Fasciitis:** 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.⁶² 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].⁶³
- **Sialorrhea, Chronic:** 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 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).⁶⁴ AAN guidelines note that botulinum toxin is probably safe and effective and should be considered (Level B).⁴⁸

- **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):** Botulinum toxin is the most widely used treatment for focal spasticity.⁶⁵ 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.⁶⁶ Several randomized, double-blind, placebo-controlled trials support the effectiveness of botulinum toxin A in the treatment of focal spasticity/focal hypertonia.^{18,67-71} 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.⁷² 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.⁷³ 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) with a minimum of eight consecutive treatments.⁷⁴ 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).^{31,75}

Dosing Considerations

Definitive dosing has not been established for off-label uses of botulinum toxins, including Botox. 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.^{1,5} The Botox prescribing information advises not to exceed 400 units of Botox in a 3-month interval.¹ Specific dosing considerations by indication are noted below:

- **Achalasia:** Botox has been studied for achalasia in several trials. Doses of 80 to 100 units of Botox were commonly used.^{2,9-11} Doses higher than 100 units of Botox per treatment have not been shown to be more effective.⁷⁶
- **Sialorrhea, Chronic:** 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.⁷⁷

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 in the ESI Coverage Review Department 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.
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2. **Cervical Dystonia (spasmodic 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.

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 prescriber; 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.

6. Spasticity, Lower 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 one of the following regimens (A or B):

A) For adults (≥ 18 years of age): Approve up to a maximum dose of 400 units (divided among 5 muscles), administered not more frequently than once every 12 weeks.

B) For pediatric patients (< 18 years of age): Approve up to a maximum dose of 8 units/kg (not to exceed 300 units), 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 one of the following regimens (A or B):

A) For adults (≥ 18 years of age): Approve up to a maximum dose of 400 units divided among selected muscles, administered not more frequently than once every 12 weeks.

B) For pediatric patients (< 18 years of age): Approve up to a maximum dose of 6 units/kg (not to exceed 200 units) 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.

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.

11. 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.

12. Chronic Low Back Pain. 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.³

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

13. Dystonia, Other than Cervical (e.g., focal dystonias, tardive dystonia, anismus, laryngeal dystonia/spasmodic dysphonia). Approve for 1 year.

(Note: For cervical dystonia, see FDA-Approved Indications criterion #2 [above]).

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

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

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

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

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

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

17. 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.

18. 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.

19. 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.

20. Sialorrhea, Chronic. Approve for 1 year.

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

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

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.⁷⁸ 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).¹³ 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.⁷⁹
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

1. Botox® for injection [prescribing information]. Madison, NJ: Allergan; October 2019.
2. Micromedex®. IBM Corporation. Available at: <http://www.micromedexsolutions.com> Accessed on May 27, 2020. Search terms: Botox.
3. Bhidayasiri R, Truong DD. Expanding use of botulinum toxin. *J Neurol Sci.* 2005;235(1-2):1-9.
4. Botox® Cosmetic [prescribing information]. Madison, NJ: Allergan Pharmaceuticals Ltd; May 2018.
5. Walker TJ, Dayan SH. Comparison and overview of currently available neurotoxins. *J Clin Aesthet Dermatol.* 2014;7(2):31-39.
6. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. *Toxins (Basel).* 2016;8(3):65.
7. Brisinda G, Bentivoglio AR, Maria G, Albanese A. Treatment with botulinum neurotoxin of gastrointestinal smooth muscles and sphincters spasms. *Mov Disord.* 2004;19(Suppl 8):S146-S156.
8. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: A review, part 1. *Am J Health Syst Pharm.* 2006;63(2):145-152.
9. Pasricha PJ, Ravich WJ, Hendrix TR, et al. Intrasphincteric botulinum toxin for the treatment of achalasia. *N Engl J Med.* 1995;332:774-778.
10. Cuillière C, Ducroté P, Zerbib F, et al. Achalasia: outcome of patients treated with intrasphincteric injection of botulinum toxin. *Gut.* 1997;41(1):87-92.
11. Annese V, Bassotti G, Coccia G, et al. and the GISMAD achalasia study group. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut.* 2000;46(5):597-600.
12. Vaezi MF, Pandolfino JF, Vela MF. ACG clinical guideline: diagnosis and management of achalasia. *Am J Gastroenterol.* 2013;108(8):1238-1249. Available at: <http://gi.org/guideline/diagnosis-and-management-of-achalasia/>. Accessed on May 27, 2020.
13. Camilleri M, Parkman HP, Shafi MA, et al. Clinical guideline: management of gastroparesis. *Am J Gastroenterol.* 2013;108(1):18-38. Available at: <http://gi.org/guideline/management-of-gastroparesis/>. Accessed on May 27, 2020.
14. Wald A, Bharucha AE, Cosman BC, et al. ACG clinical guideline: management of benign anorectal disorders. *Am J Gastroenterol.* 2014;109(8):1141-57. Available at: <http://gi.org/guideline/management-of-benign-anorectal-disorders/>. Accessed on May 27, 2020.
15. Yiannakopoulou E. Botulinum toxin and anal fissure: efficacy and safety systematic review. *Int J Colorectal Dis.* 2012;27:1-9.
16. Bansal C, Omlin KJ, Hayes CM, et al. Novel cutaneous uses for boluinum toxin type A. *J Cosmet Dermatol.* 2006; 5(3):268-272.
17. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: A review, part 2. *Am J Health Syst Pharm.* 2006;63(3):225-232.
18. Lang AM. Botulinum toxin type A therapy in chronic pain disorders. *Arch Phys Med Rehabil.* 2003;84(3 Suppl 1):S69-73.
19. von Lindem JJ, Niederhagen B, Berge S, Appel T. Type A botulinum toxin in the treatment of chronic facial pain associated with masticatory hyperactivity. *J Oral Maxillofac Surg.* 2003;61(7):774-778.

20. Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. *J Pain*. 2002;3(1):21-27.
21. Freund B, Schwartz M, Symington JM. Botulinum toxin: new treatment for temporomandibular disorders. *Br J Oral Maxillofac Surg*. 2000;38(5):466-471.
22. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. *Neurology*. 2001;56:1290-1293.
23. Jabbari B, Ney J, Sichani A, et al. Treatment of refractory, chronic low back pain with botulinum neurotoxin A: an open-label, pilot study. *Pain Med*. 2006;7(3):260-264.
24. Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. *J Neuro Neurosurg Psychiatry*. 1990;53:633-639.
25. Comella CL, Shannon KM, Jaglin J. Extensor truncal dystonia: successful treatment with botulinum toxin injections. *Mov Disord*. 1998;13:552-555.
26. Kanovsky P, Streitova H, Bares M, et al. Treatment of facial and orolingual mandibular tardive dystonia by botulinum toxin A: evidence of a long-lasting effect. *Mov Disord*. 1999;14:886-888.
27. Tarsy D, Kaufman D, Sethi KD, et al. An open-label study of botulinum toxin A for treatment of tardive dystonia. *Clin Neuropharm*. 1997;20:90-93.
28. Cole R, Hallett M, Cohen LG. Double-blind trial of botulinum toxin for treatment of focal hand dystonia. *Mov Disord*. 1995;10(4):466-471.
29. Tsui JK, Bhatt M, Calne S, Calne DB. Botulinum toxin in the treatment of writer's cramp: a double-blind study. *Neurology*. 1993;43(1):183-185.
30. Emile SH, Elfeki HA, Elbanna HG, et al. Efficacy and safety of botulinum toxin in treatment of anismus: a systematic review. *World J Gastrointest Pharmacol Ther*. 2016;7(3): 453-462.
31. Simpson DM, Blitzer A, Brashear A, et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2008;70:1699-1706. Available at: <http://www.neurology.org/content/70/19/1699.full>. Accessed on May 27, 2020.
32. Stachler RJ, Francis DO, Schwartz SR, et al. Clinical practice guideline: hoarseness (dysphonia). *Otolaryngology – Head and Neck Surgery*. 2018;Supplement:1-42. Available at: <https://journals.sagepub.com/doi/pdf/10.1177/0194599817751030>. Accessed on May 27, 2020.
33. Zesiewicz TA, Elble R, Louis ED, et al. Evidence-based guideline update: Treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2011;77:1752-1755. Available online at: <https://n.neurology.org/content/77/19/1752.abstract>. Accessed on May 27, 2020.
34. Jankovic J, Schwartz K, Clemence W, et al. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. *Mov Disord*. 1996;11:250-256.
35. Brin MF, Lyons KE, Doucette J, et al. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. *Neurology*. 2001;56:1523-1528.
36. Hertegard S, Granqvist S, Lindestad PA. Botulinum toxin injections for essential voice tremor. *Ann Otol Rhinol Laryngol*. 2000;109:204-209.
37. Adler CH, Bansberg SF, Hentz JG, et al. Botulinum toxin type A for treating voice tremor. *Arch Neurol*. 2004;61:1416-1420.
38. Pahwa R, Busenbark K, Swanson-Hyland EF, et al. Botulinum toxin treatment of essential head tremor. *Neurology*. 1995;45:822-824.
39. Lowe N, Campanati A, Bodokh I, et al. The place of botulinum toxin type A in the treatment of focal hyperhidrosis. *Br J Dermatol*. 2004;151(6):1115-1122.
40. Ferraro G, Altieri A, Grella E, D'Andrea F. Botulinum toxin: 28 patients affected by Frey's syndrome treated with intradermal injections. *Plast Reconstr Surg*. 2005;115(1):344-345.
41. Laskawi R, Drobik C, Schönebeck C. Up-to-date report of botulinum toxin type A treatment in patients with gustatory sweating (Frey's Syndrome). *Laryngoscope*. 1998;108:381-384.
42. Laccourreye O, Muscatelo L, Naude C, et al. Botulinum toxin type A for Frey's Syndrome: a preliminary prospective study. *Ann Otol Rhinol Laryngol*. 1998;107:52-55.
43. Dulguerov P, Quinodoz D, Consendai G, et al. Frey Syndrome treatment with botulinum toxin. *Otolaryngol Head Neck Surg*. 2000;122:821-827.
44. Kyrmizakis DE, Pangalos A, Papadais CE, et al. The use of botulinum toxin type A in the treatment of Frey and crocodile tears syndromes. *J Oral Maxillofac Surg*. 2004;62:840-844.
45. Naumann M, Zellner M, Toyka KV, Reiners K. Treatment of gustatory sweating with botulinum toxin. *Ann Neurol*. 1997;42(6):973-975.
46. Glaser DA. The use of botulinum toxins to treat hyperhidrosis and gustatory sweating syndrome. *Neurotox Res*. 2006;9(2-3):173-177.
47. International Hyperhidrosis Society. Primary focal craniofacial and gustatory hyperhidrosis (Frey's Syndrome). Updated January 15, 2012. Available at: <https://sweathelp.org/treatments-hcp/clinical-guidelines/primary-focal-hyperhidrosis/primary-focal-facial-and-gustatory.html>. Accessed on May 27, 2020.

48. Naumann M, So Y, Argoff CE, et al. Assessment: botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review). Report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology*. 2008;70(19):1707-1714. Available at <http://neurology.org/content/70/19/1707.full>. Accessed on May 27, 2020.
49. Walling HW, Swick BL. Treatment options for hyperhidrosis. *Am J Clin Dermatol*. 2011;12(5):285-295.
50. Haider A, Solish N. Focal hyperhidrosis: diagnosis and management. *CMAJ*. 2005;172(1):69-75.
51. Eisenach JH, Atkinson JLD, Fealey RD. Hyperhidrosis: evolving therapies for a well-established phenomenon. *Mayo Clin Proc*. 2005;80(5):657-666.
52. International Hyperhidrosis Society. Primary focal palmar hyperhidrosis. Updated January 15, 2012. Available at: <https://sweathelp.org/treatments-hcp/clinical-guidelines/primary-focal-hyperhidrosis/primary-focal-palmar.html>. Accessed on May 27, 2020.
53. International Hyperhidrosis Society. Primary focal plantar hyperhidrosis. Updated January 15, 2012. Available at: <https://sweathelp.org/treatments-hcp/clinical-guidelines/primary-focal-hyperhidrosis/primary-focal-plantar.html>. Accessed on May 27, 2020.
54. Porta M, Maggioni G. Botulinum toxin (BoNT) and back pain. *J Neurol*. 2004;251(Suppl 1):1/15-1/18.
55. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. *Pain*. 2000;85:101-105.
56. Qerama E, Fuglsang-Frederiksen, Kasch H, et al. A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. *Neurology*. 2006;67(2):241-245.
57. Ruiz MF, Moreno M, Sanchez-Garrido CM, et al. Botulinum treatment of infantile esotropia with abduction nystagmus. *J Ped Ophthalm Strabismus*. 2000;37:196-205.
58. Repka MX, Savino PJ, Reinecke RD. Treatment of acquired nystagmus with botulinum neurotoxin A. *Arch Ophthalmol*. 1994;112(10):1320-1324.
59. Leigh RJ, Tomsak RL, Grant MP, et al. Effectiveness of botulinum toxin administered to abolish acquired nystagmus. *Ann Neurol*. 1992;32(5):633-642.
60. Kao LY, Chao AN. Subtenon injection of botulinum toxin for treatment of traumatic sixth nerve palsy. *J Pediatr Ophthalmol Strabismus*. 2003;40(1):27-30.
61. Hung HL, Kao LY, Sun MH. Botulinum toxin treatment for acute traumatic complete sixth nerve palsy. *Eye*. 2005;19(3):337-341.
62. Elizondo-Rodriguez J, Araujo-Lopez Y, Moreno-Gonzalez JA, et al. A comparison of botulinum toxin A and intralesional steroids for the treatment of plantar fasciitis: a randomized, double-blinded study. *Foot Ankle Int*. 2013;34(1):8-14.
63. Thomas JL, Christensen JC, Kravitz SR, et al. The diagnosis and treatment of heel pain: a clinical practice guideline – revision 2010. *J Foot Ankle Surg*. 2010;49:S1-S19.
64. Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxin. *Toxins*. 2013;5:1010-1031.
65. Thompson AJ, Jarrett L, Lockley L, et al. Clinical management of spasticity. *J Neurol Neurosurg Psychiatry*. 2005;76(4):459-463.
66. Sulica L. Contemporary management of spasmodic dysphonia. *Curr Opin Otolaryngol Head Neck Surg*. 2004;12:543-548.
67. Brashear A, Gordon MF, Elovic E, et al for the Botox Post-Stroke Spasticity Study Group. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *NEJM*. 2002;347:395-400.
68. Koman LA, Mooney JF, Smith BP, et al. Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. BOTOX study group. *J Ped Orthopedics*. 2000;20:108-115.
69. Dunne JW, Gracies JM, Hayes M, et al. A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. *Clin Rehabil*. 2012;26(9):787-797.
70. Richardson D, Sheehan G, Werring D, et al. Evaluating the role of botulinum toxin in the management of focal hypertonia in adults. *J Neurol Neurosurgery Psychiatry*. 2000;64:499-506.
71. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for hemifacial spasm. *Cochrane Database Syst Rev*. 2005;(1):CD004899.
72. Park ES, Rha DW. Botulinum toxin type A injection for management of upper limb spasticity in children with cerebral palsy: a literature review. *Yonsei Med J*. 2006;47(5):589-603.
73. Frei K, Truong DD, Dressler D. Botulinum toxin therapy of hemifacial spasm: comparing different therapeutic preparations. *Eur J Neurol*. 2006;13(Suppl 1):30-35.
74. Kollwe K, Mohammadi B, Dengler R, Dressler D. Hemifacial spasm and reinnervation synkinesias: long-term treatment with either Botox or Dysport. *J Neural Transm*. 2010;117:759-763.
75. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86:1818-1826. Available at: <http://www.neurology.org/content/86/19/1818.full>. Accessed on May 27, 2020.
76. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2010. Available at: <http://www.clinicalpharmacology-ip.com/Default.aspx>. Accessed on May 27, 2020. Search terms: Botox.

77. Xeomin® for injection [prescribing information]. Raleigh, NC: Merz Pharmaceuticals, LLC; May 2019.
78. Ansherson RA, Pascoe L. The use of botulinum toxin-A in the treatment of patients with fibromyalgia. *J Rheumatol.* 2001; 28(7):1740.
79. Ferreira JR, Souza RP. Botulinum Toxin for Vaginismus Treatment. *Pharmacology.* 2012;89:256-259.

HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New policy	--	8/01/2018
Selected revision	Migraine prophylaxis: Added requirement to verify prior prophylactic therapies; examples of triptans added to triptan criterion.	8/22/2018
Selected revision	Dosing updated throughout policy to simplify maximum approved dosing regimens.	12/05/2018
Early annual revision	<p>Cervical Dystonia (torticollis): Clarification noted that cervical dystonia may also be called spasmodic torticollis or cervical torticollis.</p> <p>Overactive Bladder with Symptoms of Urge Urinary Incontinence, Urgency, and Frequency: Clarification noted to refer to approval condition #8 for urinary incontinence associated with a neurological condition.</p> <p>Urinary Incontinence Associated with a Neurological Condition: Clarification noted to refer to approval condition #5 for overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.</p>	05/08/2019
Annual revision	<p>FDA-Approved Uses:</p> <ul style="list-style-type: none"> • “Cervical Dystonia” updated to “Cervical Dystonia (spasmodic torticollis)”. • Under criteria for “Migraine Headache Prophylaxis in Patients with Chronic Migraine”, “prescribing physician” was updated to “prescriber”. • Pediatric dosing added for “Spasticity, Lower Limb” and “Spasticity, Upper Limb” in accordance with updated FDA labeling. <p>Other Uses with Supportive Evidence:</p> <ul style="list-style-type: none"> • “Benign Prostatic Hyperplasia” removed from policy. • “Salivary Hypersecretion” updated to “Sialorrhea, Chronic.” • “Speech/Voice Disorder (e.g., dysphonias)” renamed to laryngeal dystonia/spasmodic torticollis. This approval condition was rolled up into “Dystonia, other than cervical” and laryngeal dystonia/spasmodic dysphonia was added to the list of examples. • “Tinnitus” removed from policy. 	06/03/2020