Regence Oregon and Utah | Regence Idaho and select counties of Washington

Independent licensees of the Blue Cross and Blue Shield Association

Medication Policy Manual

Policy No: dru006

Topic: Botulinum toxin type A injection:

- Botox, onabotulinumtoxinA
- Daxxify, daxibotulinumtoxinA
- Dysport, abobotulinumtoxinA
- Xeomin, incobotulinumtoxinA

Date of Origin: January 1996

Committee Approval Date: December 12, 2024

Next Review Date: 2025

Effective Date: March 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Botulinum toxin is a neurotoxin that is injected into a muscle to cause temporary paralysis or relaxation of that muscle. There are four commercial botulinum toxin type A products available: Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Xeomin (incobotulinumtoxinA), and Daxxify (daxibotulinumtoxinA). Botulinum toxin type B (rimabotulinum, Myobloc) is covered in a separate policy.

Please note: Botulinum toxin for use in gender affirming care is covered in a separate policy, Gender-Affirming Care Products, dru757

Policy/Criteria

Most contracts require pre-authorization approval of botulinum toxin type A prior to coverage.

I. Continuation of therapy (COT): Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) may be considered medically necessary for COT when criterion A, B, or C below are met.

A. For potentially cosmetic indications, including **hyperhidrosis**, full policy criteria below must be met for coverage.

OR

B. For all other indications, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A or B below are met:

A. **Dystonia or Spastic conditions**, due to one of the following diagnoses:

1. **Cerebral Palsy**

2. **Cervical dystonia with torticollis** with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures (as documented on physical exam)

3. **Demyelinating diseases of CNS**, including, but not limited to, central demyelinating of corpus callosum, leukodystrophy, multiple sclerosis (MS), neuromyelitis optica (NMO), Schilder's disease

4. **Dysphonia**, including spasmodic dysphonia, laryngeal spasm; laryngeal adductor spastic dysphonia, or stridulus

5. **Facial nerve disorders** (such as blepharospasm, facial/hemifacial spasms, facial nerve VII disorders, facial myokymia, Melkersson syndrome)

6. **Focal upper limb/hand dystonia** (such as Organic writer's cramp)

7. **Lower limb spasticity** (including increased muscle tone in the ankle and toes)

8. **Oromandibular dystonia** (such as orofacial dyskinesia, jaw closure dystonia, Meige syndrome)
9. **Spastic hemiplegia or paraplegia** [including hereditary, related to a stroke (CVA), or related to a spinal cord injury (SCI)]
10. **Thoracic outlet syndrome**, with documentation of functional impairment.
11. **Torticollis, spasmodic or unspecified**, with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures
12. **Torsion dystonia** [including both symptomatic (acquired) or idiopathic (primary or genetic; a.k.a. Oppenheim's dystonia)]
13. **Upper limb spasticity**

OR

B. **Strabismus**, resulting in vision changes.

III. New starts (treatment-naïve patients): Botulinum toxin A (Botox, Dysport, Xeomin, Daxxify) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) for the diagnoses listed below, that one of the following criterion A through J below is met:

A. **Anal fissures,** when prior treatment with one or more therapeutic alternatives, such as nitroglycerin ointment or diltiazem cream, has been ineffective, not tolerated, or is contraindicated.

OR

B. **Congenital aganglionic megacolon (Hirschsprung disease),** with documented severe refractory constipation due to increased anal sphincter tone **or** withholding and when prior treatment with bowel regimen for constipation has been ineffective, not tolerated, or is contraindicated.

OR

C. **Endoscopically-administered botulinum,** when criteria 1 and 2 below is met:

1. An upper gastrointestinal diagnosis such as (but not limited to) **dysphagia, gastroparesis, or achalasia/cardiospasm (primary)**.

AND

2. Documented symptoms despite use of standard therapies, such as:
   - **a.** Dysphagia: Diet modification (such as smaller meals, softer foods), and/or occupational therapy.
   - **b.** Gastroparesis: Diet modification, promotility medications, such as metoclopramide, cisapride, erythromycin, or removal/reduction of underlying etiology (such as taper of opioids).
   - **c.** Achalasia/cardiospasm (primary): Dilation therapy, unless the patient is considered a poor surgical candidate.

OR

D. **Hyperhidrosis** (including axillary, palmar and gustatory hyperhidrosis), when criteria 1 through 3 below are met:

1. The hyperhidrosis is documented as persistent and severe.

AND

2. The hyperhidrosis has resulted in a significant medical complication* including a through e:

a. Acrocyanosis of the hands.

OR

b. Recurrent skin maceration with secondary bacterial or fungal infection.

OR

c. Recurrent secondary infections.

OR

d. Persistent eczematous dermatitis.

OR

e. Documentation of inability to perform critical activities of daily living or demands of employment due to hyperhidrosis.

AND

3. Treatment with at least one of the following has been ineffective, not tolerated, or all are contraindicated:

a. Prescription antiperspirants [e.g. aluminum chloride hexahydrate 20% (Drysol)].

OR

b. Oral or topical anticholinergics (e.g. glycopyrrolate or oxybutynin).

***PLEASE NOTE:** Medical treatment of persistent hyperhidrosis is considered not medically necessary in the absence of significant medical complications associated with the condition. Skin irritation, skin maceration without secondary infection, need for frequent changing of clothing, or psychosocial distress alone are not considered to be significant medical complications.

OR

E. **Migraine headache, chronic and severe,** when criteria 1 through 3 below are met:

1. A neurologist or headache specialist has thoroughly evaluated the member and has established and documented a diagnosis of chronic migraine headaches.

AND

2. Documentation of baseline headache days per month, including the number of migraines based on a headache diary OR chart notes, documenting migraine frequency, severity and characteristics.

AND

3. Documentation of an adequate trial of at least ONE prophylactic therapy, as specified in criteria a through d below were either ineffective, not tolerated, or ALL are contraindicated:

a. Topiramate **OR** divalproex sodium (Depakote).

OR

b. A beta blocker (such as propranolol, metoprolol, or atenolol).

OR

c. Venlafaxine OR a tricyclic antidepressant (such as amitriptyline or nortriptyline).

OR

d. Calcitonin gene-related peptide (CGRP) monoclonal antibody or oral CGRP antagonists [such as Aimovig (erenumab), Emgality (galcanezumab), Vyepti (eptinezumab), or Ajovy (fremanezumab), Nurtec (rimegepant), Qulipta (atogepant)] when used for prophylaxis.

PLEASE NOTE: CGRPs used for acute abortive therapy [such as "as needed" rimegepant (Nurtec ODT) or Ubrelvy (ubrogepant)] are not included in this criterion.

OR

F. **Pelvic floor dysfunction** (such as due to levator spasm, pelvic floor spasm), when criteria 1 and 2 below are met:

1. Documented pain and/or functional impairment associated with the pelvic floor dysfunction, such as pelvic pain, vaginismus, severe chronic constipation (associated with Hirschsprung's disease), dyssynergic defecation (anismus), and/or dyspareunia.

AND

2. Prior treatment with another treatment option for pelvic floor dysfunction (such as physical therapy, muscle relaxants, trigger point injections, surgery) has been ineffective, not tolerated, or is contraindicated.

OR

G. **Raynaud's syndrome or systemic sclerosis-associated digital ulcers,** when criteria 1 and 2 below is met:

1. Documented pain and/or functional impairment associated with the vasospasm and/or digital ulcers.

AND

2. Prior treatment with a dihydropyridine calcium channel blocker (such as amlodipine, nifedipine) or another vasodilator (such as topical nitroglycerin, a phosphodiesterase type 5 inhibitor, or an angiotensin II receptor blocker) has been ineffective, not tolerated, or is contraindicated.

OR

H. **Sialorrhea** (drooling).

OR

I. **Urinary incontinence,** due to detrusor overactivity [idiopathic or neurogenic (e.g. due to spinal cord injury, multiple sclerosis) or overactive bladder (OAB)], when therapy with anticholinergic agents **or** Myrbetriq (mirabegron) is ineffective or not tolerated.

OR

J. **Refractory postherpetic neuralgia (PHN)** when criteria 1 and 2 below are met:

1. Documented pain and/or functional impairment associated with postherpetic neuralgia, such as a burning, sharp, or stabbing pain that is constant or intermittent.

AND

2. Documentation that adequate trials of BOTH of the following (criteria a and b below) were either ineffective, not tolerated, or are contraindicated.

a. A gabapentinoid [such as gabapentin or pregabalin (Lyrica)].

AND

b. A tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline) OR a serotonin-norepinephrine reuptake inhibitor (SNRI, such as duloxetine or venlafaxine).

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) coverable only under the medical benefit (as a provider-administered medication).

B. **Initial Authorization**:

1. <u>For hyperhidrosis ONLY</u>: When pre-authorization is approved, botulinum toxin type A shall be authorized in quantities of up to 2 injection treatments within a 24-week period.

2. <u>For all other conditions (except as listed in 1 above)</u>: When pre-authorization is approved, botulinum toxin type A may be authorized in quantities up to 4 injection treatments within a 48-week period.

C. **Continued Authorization:**

1. After the initial authorization, up to 4 injection treatments over a 48-week period may be considered medically necessary if objective measures support clinical benefits from treatment.

2. Additional treatments may be authorized on a case-by-case basis if documentation of objective measures supporting the need for more frequent dosing are provided.

3. Coverage may be reviewed at least every 12 months to confirm that current medical necessity criteria are met and that the medication is effective, defined as sustained clinical improvement from reduced symptoms (such as pain and functional impairment).

V. Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) is considered not medically necessary for skin wrinkles or other cosmetic indications.

VI. Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) is considered investigational for all other indications, including, but not limited to:

- **A.** Allergic rhinitis.
- **B.** Benign prostatic hyperplasia.
- **C.** Congenital talipes equinovarus (clubfoot).
- **D.** Dermatochalasis (excessive eyelid skin, "baggy eyes").
- **E.** Dry eye disease.
- **F.** Headache, non-migraine (e.g. chronic daily, tension, cluster).
- **G.** Interstitial cystitis.
- **H.** Low back pain (LBP).
- **I.** Medication overuse headache (MOH).
- **J.** Motor tic disorder, chronic (including Tics associated with Tourette syndrome).
- **K.** Myofascial pain.
- **L.** Nerve entrapment or compression syndromes, other (those not listed in Section II Above: such as brachial plexus injury, carpal tunnel syndrome Piriformis syndrome).
- **M.** Obesity.
- **N.** Osteoarthritis (OA)-related pain, including of the knee.
- **O.** Plantar fasciitis pain.
- **P.** Temporomandibular dysfunction (TMJ), bruxism, and/or masseter muscle spasm.
- **Q.** Tennis elbow (lateral epicondylitis).
- **R.** Tremors [e.g. essential (benign) tremor, Parkinson's disease-related tremor].

Position Statement

- There are four botulinum toxin type A products available (abobotulinumtoxinA, daxibotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA) that all work by inhibiting the release of acetylcholine from peripheral cholinergic nerve endings, thereby blocking the cholinergic transmission.
- The intent of this policy is to allow coverage for specific diagnoses where there is demonstrated safety and efficacy from clinical trials to support their use, including spasmodic conditions, and other specific indications. Coverage for hyperhidrosis is allowed when there is documentation the condition is persistent and severe and has resulted in significant medical complications. Coverage for migraine indications is allowed when lower-cost standard of care treatment alternatives are not effective.
- There is insufficient evidence to establish that one botulinum toxin A product is more effective at comparable doses.
- Botulinum toxin type A products are all produced using different methods, so their dosing and potencies are <u>not</u> the same (the number of units of one botulinum toxin type A product cannot be converted to units of another product).

- Conditions for which use of botulinum toxin type A may be considered medically necessary are based on evidence supported by well-designed randomized controlled trials.
- The evidence for use of botulinum toxin type A in chronic migraine headache is inconsistent. Use should be reserved for those who have trialed other treatment options.
- Use of botulinum toxin (all serotypes) for treatment of wrinkles or other cosmetic conditions is considered not medically necessary.
- Botulinum toxins (type A and type B) are being investigated in many different conditions where muscle tension is thought to play a role. The quality of evidence from the majority of these studies is poor because they lack controls, are not randomized or blinded, and only involve small numbers of subjects.

Summary

CLINICAL EFFICACY

Endoscopically-administered botulinum: Achalasia (primary), Gastroparesis, and Dysphagia

- Achalasia is an esophageal motility disorder, also known as cardiospasm, which results in increased lower esophageal sphincter tone, difficulty swallowing, and sometimes regurgitation and chest pain. [1]
- Pneumatic dilation is the preferred medical treatment option for primary achalasia. [2]
- One Cochrane review concluded that pneumatic dilation produces a higher remission rate at 6 and 12 months compared to botulinum toxin. [1]
- Standard therapies for gastroparesis include diet modification (smaller meals, more frequent meals, exacerbating food avoidance), use of promotility medications, (metoclopramide, cisapride, erythromycin), and/or removal/reduction of underlying causes of gastroparesis (such as opioids).
- Approach to treatment of dysphagia (non-achalasia) is dependent on underlying pathology but may include swallowing rehabilitation (such as by a speech or occupational therapist) and/or diet modification. [3]
- Several small, poor-quality trials studied onabotulinumtoxinA in the treatment of gastroparesis. Improvement in gastric emptying time was inconsistent with some trials showing possible benefit [4] and others showing no benefit. [5 6] Despite inconclusive benefit of onabotulinumtoxinA, there is a lack of robust evidence for management of refractory gastroparesis for any one treatment approach. Therefore, botulinum toxin A may be considered medically necessary when standard initial therapies are ineffective. [7]

Anal Fissures

- Nitroglycerin ointment, diltiazem cream, and onabotulinumtoxinA have been studied in the treatment of anal fissures.
    * Nitroglycerin ointment and topical calcium channel blocker (e.g. diltiazem or nifedipine) cream are the least invasive.
    * Several small studies suggest healing rates of up to 70% with onabotulinumtoxinA. [8]
    * Trials comparing nitroglycerin ointment with onabotulinumtoxinA show inconsistent results.

    - A comparative trial demonstrated a healing rate of 52% with nitroglycerin compared to 24% with onabotulinumtoxinA after 2 weeks of treatment. [9]
    - A second comparative trial demonstrated a healing rate of 60% with nitroglycerin ointment compared to 96% with onabotulinumtoxinA. [10]
    - Another study in 73 subjects with anal fissure found there were no advantages of onabotulinumtoxinA over nitroglycerin ointment in fissure healing and fissure-related pain. [11]
    - A Cochrane review concluded topical CCBs, nitroglycerin and botulinum toxin to be overall similarly effective non-surgical treatment options. However, surgical sphincterotomy remains the most efficacious therapy; however, it is limited by significant risks. [8]
* A small randomized, double-blind, controlled trial comparing diltiazem cream to onabotulinumtoxinA showed no difference in fissure healing between groups after three months of treatment. [12]

Congenital aganglionic megacolon (Hirschsprung disease)[13-16]

- Congenital aganglionic megacolon (Hirschsprung disease) is a rare gastrointestinal disorder, due to incomplete neuronal development in the distal colon, resulting in abnormal bowel function due to increased/decreased anal sphincter tone or withholding. The condition is generally diagnosed in children and can result in fecal incontinence, constipation, and enterocolitis.
- For constipation symptoms due to increased anal sphincter tone or withholding, treatment options include standard bowel regimen, botulinum toxin, and surgery. There is no standard sequencing of therapies; however, the goal of conservative therapies, including botulinum, includes avoidance of surgical procedures.

Cervical dystonia (spasmodic torticollis)

- Cervical dystonia (or spasmodic torticollis) is characterized by involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures. [17]
- A Cochrane review concluded a significant decrease in the cervical dystonia severity scale (CDSS) along with an improved physician's global assessment score and reduction in pain after use of onabotulinumtoxinA injection relative to placebo. The CDSS is an objective measurement used to quantify the severity of abnormal head positioning that results from cervical dystonia. [17]
- OnabotulinumtoxinA has not been shown to be effective in the treatment of in chronic neck pain without torticollis (with or without cervicogenic headache) and mechanical neck disorders and whiplash. [18 19]

Migraine Headache

- The International Headache Society (IHS) Classification of Chronic Migraine Headache's definition of chronic migraine includes that headaches are present on 15 days or more per month, and that at least 8 of these episodes meet the criteria for pain and associated symptoms of migraine (*Appendix 1*).
- The U.S. Headache Consortium endorses headache calendars as the gold standard to track treatment progress. [20]

- Evidence supporting the efficacy of botulinum toxin A in the treatment of migraines has been inconsistent.[21]
- Collective results of seven randomized, controlled episodic migraine trials (totaling more than 1,000 patients) have failed to demonstrate a significant difference between botulinum toxin A and placebo in migraine prevention. Pre-specified primary endpoints and most secondary endpoints were not met. [22-26]
- Two additional trials studying onabotulinumtoxinA in the treatment of chronic migraine were more recently published. [27 28]
    * In the PREEMPT 1 trial, there was no difference between placebo and onabotulinumtoxinA in mean change in headache episodes, the primary endpoint.
    * In the PREEMPT 2 trial, the primary endpoint was changed to mean change in headache days after the PREEMPT 1 trial failed to meet its primary endpoint. A statistical difference favoring onabotulinumtoxinA over placebo was demonstrated. The mean number of headaches decreased from approximately 20 to 11 in the onabotulinumtoxinA group and from approximately 20 to 13 in the placebo group at week 24.
    * Subjects enrolled in the trials had migraine headaches occurring on 15 or more days per 4 weeks, of which each consisted of four or more hours of continuous headache.
- The American Academy of Neurology (AAN) 2016 guideline update supports the use of botulinum toxin type A products in the prevention or treatment of chronic migraine headaches[21]. The AAN Assessment of botulinum toxin A concludes that:
    * They are likely effective in chronic migraine headaches and should be offered as a treatment option to increase the number of headache-free days.
    * They are likely ineffective in treatment of episodic migraine and chronic tension-type headache
- Both the AAN and the American Headache Society recommend limiting the use of abortive therapies for headache. These include over-the-counter (OTC) medications such as NSAIDS and acetaminophen, given the risk of developing medication overuse headache (MOH). Use of OTC abortives should be limited to no more than 14 days per month. In addition, use of butalbital-containing medications and opioids can increase sensitivity to pain. Use of these prescription abortives should be limited to no more than nine days per month (or two days per week). [29]

  Use of Oral Prophylactic Therapies [30 31]
    * Guidelines from the American Academy of Neurology and American Headache Society recommend select antiepileptic medications (divalproex or topiramate) and beta-blockers (propranolol, timolol, or metoprolol) as options that should be offered to patients requiring migraine prophylaxis, with the highest level of evidence to support their use.
    * Other medications that are “probably effective and should be considered” include tricyclic antidepressant (TCA) amitriptyline, selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, atenolol and nadolol.

* Use of carbamazepine and a variety of select antihypertensives (candesartan, lisinopril, clonidine, guanfacine, or pindolol) are possibly effective; however, the many other prophylactic alternatives with higher-quality evidence should be used first.
* Many other medications, including but not limited to selective serotonin receptor inhibitors (SSRIs; e.g. fluoxetine, fluvoxamine), other SNRIs (e.g. duloxetine), other AEDs (gabapentin, lamotrigine, and oxcarbazepine), calcium channel blockers (CCBs; e.g. nicardipine, nifedipine, verapamil) and clonazepam, have been studied in migraine prophylaxis, but evidence supporting their efficacy is conflicting, inadequate, or negative (support the therapy is ineffective). [30 31]
* There is insufficient evidence directly comparing botulinum toxin A with other prophylactic therapies such as beta-blockers, antiepileptic medications, tricyclic antidepressants, calcitonin gene-related peptide (CGRP) monoclonal antibodies, or oral CGRP antagonists . [7]

Other Types of Headaches:

* Chronic Daily Headache (CDH): botulinum toxin A has not been shown to be effective in treatment or prevention of CDH.[21 23 32 33]
* Tension Headache: Current evidence is insufficient to permit conclusions regarding botulinum toxin type A products as prophylactic therapy in patients with chronic tension headaches refractory to pharmacologic therapy. [21 22 34-37]
* Current evidence is insufficient to allow the use of botulinum toxin A in the treatment of episodic migraine headaches, tension headaches, or chronic daily headaches [21 34 36-38]

Hyperhidrosis

- Hyperhidrosis can lead to medical complications, including skin maceration with recurrent bacterial or fungal infection requiring treatment or persistent eczematous dermatitis. [39]
- Palmar hyperhidrosis can interfere with ability to function, when grip is impaired due to hyperhidrosis. [39]
- Topical treatments, such as aluminum chloride solution (Drysol) are the primary therapy for axillary and palmar hyperhidrosis, once secondary causes of hyperhidrosis are ruled out. Topical treatments and systemic anticholinergics are primary therapy for persistent eczematous dermatitis. [39]
- There are several double-blind trials that evaluate onabotulinumtoxinA in patients with primary axillary and primary palmar hyperhidrosis. [7 40 41]
  * Treated palms with onabotulinumtoxinA were associated with a 26% reduction in sweating (measured by ninhydrin sweat testing) compared to no reduction with placebo. [40]
  * In two pivotal trials, 81% to 91% of patients treated for primary axillary hyperhidrosis achieved a greater than 50% reduction in axillary sweating at 4 weeks compared with 36% to 41% in the placebo group. [7]
- The median duration of effect in two pivotal trials that evaluated onabotulinumtoxinA in primary axillary hyperhidrosis was 201 days. [7]

- Reduction in sweating is also described in case series reports for both palmar and axillary hyperhidrosis with onabotulinumtoxinA injections lasting up to 5-12 months. [42 43]
- However, despite the reduction in sweating, onabotulinumtoxinA does not affect the unpleasant odor.
- In a small case study, intracutaneous onabotulinumtoxinA was effective in ceasing gustatory sweating up to a mean duration of 17 months. [44]

Muscle Spasms and Dystonias

- A spasm is defined as a sudden involuntary contraction of one or more muscles.
- Muscle spasms are a potential symptom of spasticity, a condition in which specific muscles are continuously contracted. The contraction causes muscles to be stiff or tight and may interfere with movement, speech, and walking.
- Botulinum has been studied and shown to be effective in spasticity due to cerebral palsy,[45 46] spastic hemiplegia or paraplegia,[47] dysphonia,[7 48], blepharospasm,[49] hemifacial spasm,[50] facial nerve disorders, and demyelinating disease of the CNS,[7 51], as well as a variety of dystonias: hand dystonia, [7] oromandibular dystonia,[7] spasmodic torticollis,[7] and torsion dystonia [7].

Pelvic Floor Dysfunction, including levator (pelvic floor) spasm

- Pelvic floor dysfunction is global term used to describe a number of conditions, including chronic pelvic pain. For pelvic floor dysfunction due to levator (pelvic floor) muscle spasm, non-pharmacologic therapy includes physical therapy with pelvic floor training can be used, along with other types of physical therapy. Pharmacologic therapies include various chronic pain medications such as antiepileptics, antidepressants (tricyclic, serotonergic), muscle relaxants, NSAIDs, as well as hormone replacement therapies. Opioids may be used for severe pain, along with trigger point injections. Surgery is reserved for refractory pain. [52]
- The evidence for onabotulinumtoxinA for treatment of pelvic floor muscle spasm is limited to one randomized controlled trial (n=60). The trial reported a decrease in pelvic floor muscle pressure but no significant difference reduction in pain scores.[52] However, there is a lack of robust evidence for management of refractory pelvic floor muscle spasm for any one treatment approach. Therefore, botulinum toxin A may be considered medically necessary when standard initial therapies are ineffective.

Raynaud's Disease

- Raynaud's phenomenon (Raynaud disease) is vasospasm due to cold or stress and can lead to severe constriction of the digits (both fingers and toes). Severe cases may result in digital ischemia, ulcers, and gangrene. [53]
- Non-pharmacologic therapy includes trigger avoidance, including cold, vasoconstricting medications, and smoking. Pharmacologic therapies may be used for refractory RP.
- Dihydropyridine calcium channel blockers (CCBs), such as amlodipine or nifedipine, are the usual first-line pharmacologic treatment options. Other pharmacologic treatment options include various vasodilators: phosphodiesterase (PDE) type 5 inhibitor (e.g. sildenafil, tadalafil), topical nitroglycerin, an angiotensin receptor blocker (e.g. losartan, valsartan), or a serotonin reuptake inhibitor.

- There is limited evidence to guide the management of refractory or progressive ischemia. The goal is prevention of tissue loss, including amputation of digits. Treatment may include aggressive non-pharmacologic, pharmacologic, and surgical therapies. [54]
- The evidence for onabotulinumtoxinA or incobotulinumtoxinA for treatment of Raynaud's syndrome is limited to one pilot trial and one retrospective case series with onabotulinumtoxinA. [88-90] However, given the lack of non-surgical options for refractory ulcers, botulinum toxin A may be covered when standard vasodilator therapy is ineffective, not tolerated, or all options are documented as medically contraindicated.

Sialorrhea (drooling)

- Botulinum toxin A or B can be used for reduction of sialorrhea in patients with a variety of neurological disorders. The goal of therapy is to reduce sialorrhea -associated complications, such as aspiration pneumonia or skin breakdown.
- Anatomically guided injections of rimabotulinumtoxinB into the parotid and submandibular glands appear to effectively improve sialorrhea in patients with a variety of neurologic conditions, including Parkinson's disease and amyotrophic lateral sclerosis (ALS). [7 55 56]

Thoracic Outlet Syndrome

- Thoracic outlet syndrome (TOS) is a form of myofascial pain and may include brachial plexus injury.
    * A Cochrane review concluded that there is insufficient evidence to conclude that botulinum toxin is effective for treatment of TOS. [57] In one small trial, botulinum toxin did not significantly reduce pain or disability scores versus placebo in patients with TOS (of any type). The evidence is complicated by a lack of consensus in the diagnosis of TOS. Additional research is needed to clarify the benefit of TOS treatments.[58]
    * Strengthening exercises, physical therapy and surgery are the standard of care. In patients, in whom these options have been ineffective, botulinum toxin may be a treatment option.

Urinary Incontinence - Neurogenic and idiopathic detrusor overactivity/detrusor hyperreflexia

- Several open-label studies (n=15 to n=200) demonstrated an increase in bladder capacity, a decrease in bladder pressure, and a decrease in incontinence episodes after injection with onabotulinumtoxinA, in both children and adults.[59-61]
- A Cochrane review concluded both botulinum type A and B formulations are effective treatment options for urinary incontinence due to refractory detrusor overactivity due to neurogenic or idiopathic overactive bladder (OAB). [62]

Refractory Postherpetic Neuralgia (PHN) [63]

- Refractory postherpetic neuralgia (PHN) refers to pain that persists after an acute episode of herpes zoster and resolution of the rash. PHN affects nerve fibers and skin and is characterized by constant burning, stabbing sensation or pain triggered by light contact with non-painful stimuli, resulting in decreased quality of life.
- First-line pharmacologic therapies for PHN include topical lidocaine, gabapentinoids (gabapentin, pregabalin), tricyclic antidepressants (TCAs; amitriptyline, nortriptyline), and serotonin-norepinephrine reuptake inhibitors (SNRIs; duloxetine and venlafaxine).

- A systematic review and meta- analysis of seven trials with a total of 752 patients concluded that botulinum toxin A has a greater efficacy than lidocaine for postherpetic neuralgia, based on the visual analog scale (VAS) of these 7 trials. [64]
- For refractory PHN, in which first-line standard of care pharmacologic treatment options have been ineffective, botulinum toxin A may be a treatment option for these patients.

INVESTIGATIONAL USES

Allergic Rhinitis

- One small (n=34) randomized controlled trial of 8-week duration suggests efficacy of onabotulinumtoxinA in relieving rhinorrhea, nasal obstruction and sneezing due to allergic rhinitis. There was no difference between onabotulinumtoxinA and placebo groups for the symptom of itching. [65]
- Well-designed, large-scale trials with repeated injections and comparison to nasal steroids are necessary to validate positive benefits of using onabotulinumtoxinA in this condition.

Benign Prostatic Hyperplasia (BPH)

- A small, poor-quality trial comparing the effects of onabotulinumtoxinA with or without an alpha-adrenergic antagonist suggest possible onabotulinumtoxinA efficacy. The absence of a placebo comparator makes it difficult to determine the true efficacy of onabotulinumtoxinA. [66] The evidence for the use of onabotulinumtoxinA in the treatment of BPH is limited to a variety of Phase II and uncontrolled trials. [7 67] Additional higher-quality studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition.

Congenital talipes equinovarus (clubfoot) [68]

- A Cochrane review concluded that there is insufficient evidence to conclude that botulinum toxin is effective for treatment of clubfoot. The evidence is limited to one small trial, as adjunctive therapy to casting.
- Usual conservative interventions include stretching, casting, and splinting. Surgery is reserved for resistant deformities.

Dermatochalasis

- Dermatochalasis is a condition in which a fold of skin develops in the eyelid, potentially leading to impaired vision, blepharitis, and dermatitis. Surgery is the current standard of care.
- A small, poor-quality study (open-label study without a placebo comparator) suggests that onabotulinumtoxinA may be an effective treatment for upper eyelid dermatochalasis. [69] Additional well-controlled studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition.

Dry Eye Disease

- The evidence for the use of onabotulinumtoxinA for dry eye disease is limited to one small pilot trial (n=20). [70] Larger, well-controlled trials are needed to establish safety and effectiveness of onabotulinumtoxinA for this indication.

Interstitial Cystitis

- Four, poor-quality studies (case series) have assessed onabotulinumtoxinA treatment for pain and improvement of bladder capacity in patients with interstitial cystitis. All

reports suggest efficacy, though results have not been confirmed in larger controlled trials. [7 71]

Low Back Pain

- The evidence for the use of botulinum toxin A in the treatment of lower back pain is limited to several small, poor-quality trials. [72] The studies did not address functional improvement or long-term effects of onabotulinumtoxinA. Large, well-controlled studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition. [7]

Motor Tics

- In one small, poor-quality trial, onabotulinumtoxinA reduced tic frequency and urge in patients with Tourette Syndrome or Chronic Tic Disorder. [73] These reductions were not associated with an overall clinical benefit (measured by the patient's global impression of change).

Myofascial Pain

- OnabotulinumtoxinA has not been shown to provide a consistent benefit over placebo in the treatment of myofascial pain. [7 74]
- One small trial found botulinum toxin A improved pain and quality of life. However, small trial size and use of an enriched protocol design limit generalizability of findings to clinical practice. Only half of patients responded to the initial dose of botulinum toxin A and were enrolled in the randomized phase of the trial. [75]

Obesity

- There is no reliable evidence that onabotulinumtoxinA is useful in reducing body weight in obese patients.
    * Two small, poor-quality trials failed to show a reduction in body weight after administration of onabotulinumtoxinA. [76 77]
    * A small randomized, double-blind study in 24 morbidly obese patients demonstrated significant difference between onabotulinumtoxinA and saline. However, patients were also maintained on a liquid diet for eight weeks. [78]

Orthopedic Pain – Plantar Fasciitis, Lateral epicondylitis (tennis elbow), Osteoarthritis (OA) of the knee

- Four small, exploratory randomized controlled trials reported an improvement in pain scores with onabotulinumtoxinA in patients with plantar fasciitis refractory to other therapies. [79-82]
- Several small, poor-quality trials evaluated onabotulinumtoxinA in patients with lateral epicondylitis (tennis elbow). [83-85] Consistent benefit has not been demonstrated across trials.
- One trial evaluated intra-articular onabotulinumtoxinA for treatment of OA-related knee pain. [86] Despite a reduction in pain with onabotulinumtoxinA versus placebo, additional evidence is needed to establish the clinical benefit versus established standard of care treatments for OA, such as NSAIDs.
- Larger, well-controlled trials are needed to establish safety and effectiveness in these conditions and to establish efficacy relative to conventional therapies. [7]

Nerve Entrapment and Compression Syndromes (such as Brachial Plexus Injury, Carpal Tunnel Syndrome, Piriformis Syndrome)

- Piriformis syndrome is a form of myofascial pain characterized by sciatica and buttock tenderness.
    * Few case reports describe the management of piriformis syndrome. [87] Physical therapy, steroid injections, surgical dissection or resection of the muscle have been reported to relieve symptoms.
    * Well-designed studies using onabotulinumtoxinA for this condition have not been conducted. Available evidence consists of small (fewer than 30 patients) open-label, uncontrolled studies. [7 88]
- There is insufficient evidence to establish efficacy of botulinum toxin for treatment of carpal tunnel syndrome. The evidence is limited to one pilot trial. [89]

Temporomandibular dysfunction (TMJ), Bruxism, and/or Masseter Muscle Spasm and Hypertrophy

- Several small, uncontrolled (case series) studies have studied onabotulinumtoxinA in the treatment of symptoms (headache, jaw dislocation, etc.) arising from TMJ dysfunction. Larger, well-controlled studies are needed to establish benefit in the treatment of this condition. [90-93]
- Several small, poor-quality trials evaluated onabotulinumtoxinA in patients with bruxism, masseter muscle spasm, and/or masseter hypertrophy and one small trial with incobotulinumtoxinA. Consistent benefit has not been demonstrated across trials. Additional larger trials are needed to establish the safety and efficacy of botulinum toxin type A. [94-98]

Tremor

- There is insufficient evidence to support the use of onabotulinumtoxinA in essential hand tremor or MS-related tremor and no evidence in Parkinson's disease-related tremor. [7 99]
- OnabotulinumtoxinA resulted in significant improvement of postural, but not kinetic essential hand tremors. [99] Likewise, one small crossover trial of incobotulinumtoxinA (n=30) improved rest tremor, tremor severity, and postural tremor. [100] However, there is not compelling evidence that either botulinum toxin formulation leads to better functional efficacy for patients.

SAFETY

- The severity and type of adverse effects depends on the location where the botulinum toxin A is injected, the dose used, and the injection technique.
- Commonly reported adverse events observed in clinical trials of onabotulinumtoxinA include dry mouth, dysphagia, asthenia, diplopia, and injection site pain. The prevalence and severity of adverse effects may vary depending on the dose and the site of injection. [51]
- All botulinum toxin products carry a box warning in their labeling describing the potential for toxin to spread from the site of injection and produce symptoms consistent with botulinum toxin effects. Symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties and may occur hours to weeks after injection.

Swallowing and breathing difficulties can be life threatening. Deaths have been reported.

- The safety, efficacy and dosing of botulinum toxins has not been established for any condition in children less than 12 years of age.

DOSING CONSIDERATIONS

- Botulinum toxin type A products are all produced using different methods, so their dosing and potencies are not the same (the number of units of one botulinum toxin type A product cannot be converted to units of another product).
- Starting doses for botulinum toxin type A products are available in the prescribing information for the specific products. Follow-up doses may be adjusted based on the effectiveness of the initial injections and adverse effects.

Appendix 1: International Headache Society Classification of Chronic Migraine Headache [101]

A. Headache (tension-type and/or migraine) on 15 or more days per month for at least 3 months.*

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for a migraine without an aura.

C. On 8 or more days per month for at least 3 months headache has fulfilled criteria for pain and associated symptoms of migraine without aura in either or both of criteria 1 head 2 below:

1. At least two of the following criteria a, b, c, and d below are met:

a) Unilateral location.

b) Pulsating quality.

c) Moderate or severe pain intensity.

d) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs).

AND at least one of the following criteria e or f below are met:

e) Nausea and/or vomiting.

f) Photophobia and phonophobia.

2. Treated and relieved by triptan(s) or ergot before the expected development of the above symptoms.

D. No medication overuse and not attributed to another causative disorder.

* Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least one month. Sample diaries are available at http://www.i-h-s.org.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.05 - Label Use of Botulinum Toxin. [November 2023]
BlueCross BlueShield Association Medical Policy, 8.01.19 - Treatment of Hyperhidrosis. [July 2023]
Surgical Treatments for Hyperhidrosis, Medical Policy Manual; Med 165.
Myobloc, rimabotulinumtoxinB, Medication Policy Manual, Policy No. dru048
Oral CGRP antagonists and 5-HT 1f agonists, Medication Policy Manual, Policy No. dru635
CGRP Monoclonal Antibodies, Medication Policy Manual, Policy No. dru540
Cosmetic and Reconstructive Surgery, Medical Policy Manual; Surgery, Policy No. 12.
Gender-Affirming Care Products, Medication Policy Manual, Policy No. dru757

Codes	Number	Description
HCPCS	J0585	Injection, onabotulinumtoxinA (Botox), 1 unit
HCPCS	J0586	Injection, abobotulinumtoxinA (Dysport), 5 Units
HCPCS	J0588	Injection, incobotulinumtoxinA (Xeomin), 1 unit
		Injection, daxibotulinumtoxinA (Daxxify)

References

1. Leyden JE, Moss AC,MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. *The Cochrane database of systematic reviews*. 2014;12:CD005046. PMID: 25485740
2. Committee ASoP, Pasha SF, Acosta RD, et al. The role of endoscopy in the evaluation and management of dysphagia. *Gastrointestinal endoscopy*. 2014;79(2):191-201. PMID: 24332405
3. Talley NJ. Oropharyngeal dysphagia: Clinical features, diagnosis, and management. Last updated Feb 2020. . In: Lembo AJ, ed. . ed. Waltham, MA: UpToDate, 2020.
4. Lacy BE, Crowell MD, Schettler-Duncan A, et al. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. *Diabetes care*. 2004;27(10):2341-7. PMID: 15451898
5. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. *Alimentary pharmacology & therapeutics*. 2007;26(9):1251-8. PMID: 17944739
6. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum toxin A for the treatment of delayed gastric emptying. *The American journal of gastroenterology*. 2008;103(2):416-23. PMID: 18070232
7. "Botulinum Toxin." BlueCross BlueShield Association (BCBSA) Medical Policy Reference Manual, Policy No. 5.01.05, Last review date: September 2013
8. Nelson RL, Thomas K, Morgan J, et al. Non surgical therapy for anal fissure. *The Cochrane database of systematic reviews*. 2012;2:CD003431. PMID: 22336789

9. Fruehauf H, Fried M, Wegmueller B, et al. Efficacy and safety of botulinum toxin a injection compared with topical nitroglycerin ointment for the treatment of chronic anal fissure: a prospective randomized study. *The American journal of gastroenterology.* 2006;101(9):2107-12. PMID: 16848808

10. Brisinda G, Maria G, Bentivoglio AR, et al. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *The New England journal of medicine.* 1999;341(2):65-9. PMID: 10395629

11. Festen S, Gisbertz SS, van Schaagen F, et al. Blinded randomized clinical trial of botulinum toxin versus isosorbide dinitrate ointment for treatment of anal fissure. *The British journal of surgery.* 2009;96(12):1393-9. PMID: 19918859

12. Samim M, Twigt B, Stoker L, et al. Topical diltiazem cream versus botulinum toxin a for the treatment of chronic anal fissure: a double-blind randomized clinical trial. *Annals of surgery.* 2012;255(1):18-22. PMID: 21685792

13. Wester T,Granstrom AL. Botulinum toxin is efficient to treat obstructive symptoms in children with Hirschsprung disease. *Pediatric surgery international.* 2015;31(3):255-9. PMID: 25616563

14. Wesson DE. Congenital aganglionic megacolon (Hirschsprung disease). Last updated Nov. 9, 2016. . In: Singer JI, ed. Waltham, MA: UpToDate, 2016.

15. Zani A, Eaton S, Morini F, et al. European Paediatric Surgeons' Association Survey on the Management of Hirschsprung Disease. *European journal of pediatric surgery : official journal of Austrian Association of Pediatric Surgery [et al] = Zeitschrift fur Kinderchirurgie.* 2016. PMID: 27898990

16. Thakkar HS, Bassett C, Hsu A, et al. Functional outcomes in Hirschsprung disease: A single institution's 12-year experience. *Journal of pediatric surgery.* 2016. PMID: 27912977

17. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for cervical dystonia. *The Cochrane database of systematic reviews.* 2005(1):CD003633. PMID: 15674910

18. Langevin P, Peloso PM, Lowcock J, et al. Botulinum toxin for subacute/chronic neck pain. *The Cochrane database of systematic reviews.* 2011(7):CD008626. PMID: 21735434

19. Peloso P, Gross A, Haines T, et al. Medicinal and injection therapies for mechanical neck disorders. *The Cochrane database of systematic reviews.* 2007(3):CD000319. PMID: 17636629

20. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;55(6):754-62. PMID: 10993991

21. 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. United States, 2016:1818-26. PMID: 27164716

22. Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. *Headache.* 2000;40(6):445-50. PMID: 10849039

23. Evers S, Vollmer-Haase J, Schwaag S, et al. Botulinum toxin A in the prophylactic treatment of migraine--a randomized, double-blind, placebo-controlled study. *Cephalalgia : an international journal of headache.* 2004;24(10):838-43. PMID: 15377314

24. Elkind AH, O'Carroll P, Blumenfeld A, et al. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. *The journal of pain : official journal of the American Pain Society.* 2006;7(10):688-96. PMID: 17018329

25. Relja M, Poole AC, Schoenen J, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. *Cephalalgia : an international journal of headache.* 2007;27(6):492-503. PMID: 17428299

26. Aurora SK, Gawel M, Brandes JL, et al. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. *Headache.* 2007;47(4):486-99. PMID: 17445098

27. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia : an international journal of headache.* 2010;30(7):793-803. PMID: 20647170

28. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia : an international journal of headache.* 2010;30(7):804-14. PMID: 20647171

29. Choosing Wisely. Lists: Treating Migraine Headaches.February 2013. [cited 1/12/2017]. 'Available from:' http://www.choosingwisely.org/doctor-patient-lists/treating-migraine-headaches/.

30. Loder E, Burch R,Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache.* 2012;52(6):930-45. PMID: 22671714

31. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology.* 2012;78(17):1337-45. PMID: 22529202

32. Silberstein SD, Stark SR, Lucas SM, et al. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. *Mayo Clinic proceedings.* 2005;80(9):1126-37. PMID: 16178492

33. Silberstein SD, Gobel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. *Cephalalgia : an international journal of headache.* 2006;26(7):790-800. PMID: 16776693

34. Schulte-Mattler WJ, Krack P,Bo NSG. Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. *Pain.* 2004;109(1-2):110-4. PMID: 15082132

35. Ondo WG, Vuong KD,Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. *Cephalalgia : an international journal of headache.* 2004;24(1):60-5. PMID: 14687015

36. Padberg M, de Bruijn SF, de Haan RJ, et al. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. *Cephalalgia : an international journal of headache.* 2004;24(8):675-80. PMID: 15265057

37. Rollnik JD, Tanneberger O, Schubert M, et al. Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. *Headache.* 2000;40(4):300-5. PMID: 10759934

38. Straube A, Empl M, Ceballos-Baumann A, et al. Pericranial injection of botulinum toxin type A (Dysport) for tension-type headache - a multicentre, double-blind, randomized, placebo-controlled study. *European journal of neurology : the official journal of the European Federation of Neurological Societies.* 2008;15(3):205-13. PMID: 18290842

39. "Treatment of Hyperhidrosis." BlueCross BlueShield Association (BCBSA) Medical Policy Reference Manual, Policy No. 5.01.05, Last review date: May 2013

40. Schnider P, Binder M, Auff E, et al. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. *The British journal of dermatology.* 1997;136(4):548-52. PMID: 9155956

41. Lowe NJ, Glaser DA, Eadie N, et al. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. *Journal of the American Academy of Dermatology.* 2007;56(4):604-11. PMID: 17306417

42. Naumann M. Evidence-based medicine: botulinum toxin in focal hyperhidrosis. *Journal of neurology.* 2001;248 Suppl 1:31-3. PMID: 11357238

43. Shelley WB, Talanin NY,Shelley ED. Botulinum toxin therapy for palmar hyperhidrosis. *Journal of the American Academy of Dermatology.* 1998;38(2 Pt 1):227-9. PMID: 9486678

44. Laskawi R, Drobik C,Schonebeck C. Up-to-date report of botulinum toxin type A treatment in patients with gustatory sweating (Frey's syndrome). *The Laryngoscope.* 1998;108(3):381-4. PMID: 9504611

45. Ade-Hall RA,Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. *The Cochrane database of systematic reviews.* 2000(2):CD001408. PMID: 10796784

46. Hoare BJ, Wallen MA, Imms C, et al. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). *The Cochrane database of systematic reviews.* 2010(1):CD003469. PMID: 20091546

47. Demetrios M, Khan F, Turner-Stokes L, et al. Multidisciplinary rehabilitation following botulinum toxin and other focal intramuscular treatment for post-stroke spasticity. *The Cochrane database of systematic reviews.* 2013;6:CD009689. PMID: 23740539

48. Watts CC, Whurr R,Nye C. Botulinum toxin injections for the treatment of spasmodic dysphonia. *The Cochrane database of systematic reviews.* 2004(3):CD004327. PMID: 15266530

49. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for blepharospasm. *The Cochrane database of systematic reviews.* 2005(1):CD004900. PMID: 15674969

50. Costa J, Espirito-Santo C, Borges A, et al. Botulinum toxin type A therapy for hemifacial spasm. *The Cochrane database of systematic reviews.* 2005(1):CD004899. PMID: 15674968

51. Botox® (onabotulinumtoxinA) [package insert]. Irvine, CA: Allergan, Inc; August 2023

52. Moynihan LK. Treatment of myofascial pelvic pain syndrome in women. Last updated Feb. 2020. In: Brubaker L, ed. . ed. Waltham, MA: UpToDate, 2020.

53. Wigley FM. Treatment of Raynaud phenomenon: Initial management. Last updated Feb 2020. In: Axford J, ed. . ed. Waltham, MA: UpToDate, 2020.

54. Wigley FM. Treatment of Raynaud phenomenon: Refractory or progressive ischemia. Last updated Feb 2020. In: Axford J, ed. . ed. Waltham, MA: UpToDate, 2020.

55. Young CA, Ellis C, Johnson J, et al. Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. *The Cochrane database of systematic reviews.* 2011(5):CD006981. PMID: 21563158

56. Mancini F, Zangaglia R, Cristina S, et al. Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. *Movement disorders : official journal of the Movement Disorder Society.* 2003;18(6):685-8. PMID: 12784273

57. Povlsen B, Hansson T,Povlsen SD. Treatment for thoracic outlet syndrome. *The Cochrane database of systematic reviews.* 2014;11:CD007218. PMID: 25427003

58. Jordan SE, Ahn SS, Freischlag JA, et al. Selective botulinum chemodenervation of the scalene muscles for treatment of neurogenic thoracic outlet syndrome. *Annals of vascular surgery*. 2000;14(4):365-9. PMID: 10943789

59. Kajbafzadeh AM, Moosavi S, Tajik P, et al. Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. *Urology*. 2006;68(5):1091-6; discussion 96-7. PMID: 17113899

60. Riccabona M, Koen M, Schindler M, et al. Botulinum-A toxin injection into the detrusor: a safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. *The Journal of urology*. 2004;171(2 Pt 1):845-8; discussion 48. PMID: 14713840

61. Smith CP, Somogyi GT,Boone TB. Botulinum toxin in urology: evaluation using an evidence-based medicine approach. *Nature clinical practice Urology*. 2004;1(1):31-7. PMID: 16474464

62. Duthie JB, Vincent M, Herbison GP, et al. Botulinum toxin injections for adults with overactive bladder syndrome. *The Cochrane database of systematic reviews*. 2011(12):CD005493. PMID: 22161392

63. Mallick-Searle T, Snodgrass B,Brant JM. Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. J Multidiscip Healthc. New Zealand, 2016:447-54. PMID: 27703368

64. Li XL, Zeng X, Zeng S, et al. Botulinum toxin A treatment for post-herpetic neuralgia: A systematic review and meta-analysis. Exp Ther Med. Greece, 2020:1058-64. PMID: 32010269

65. Unal M, Sevim S, Dogu O, et al. Effect of botulinum toxin type A on nasal symptoms in patients with allergic rhinitis: a double-blind, placebo-controlled clinical trial. *Acta oto-laryngologica*. 2003;123(9):1060-3. PMID: 14710908

66. Park DS, Cho TW, Lee YK, et al. Evaluation of short term clinical effects and presumptive mechanism of botulinum toxin type A as a treatment modality of benign prostatic hyperplasia. *Yonsei medical journal*. 2006;47(5):706-14. PMID: 17066515

67. Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *European urology*. 2013;64(1):118-40. PMID: 23541338

68. Gray K, Pacey V, Gibbons P, et al. Interventions for congenital talipes equinovarus (clubfoot). *The Cochrane database of systematic reviews*. 2014;8:CD008602. PMID: 25117413

69. Cohen JL,Dayan SH. Botulinum toxin type a in the treatment of dermatochalasis: an open-label, randomized, dose-comparison study. *Journal of drugs in dermatology : JDD*. 2006;5(7):596-601. PMID: 16865863

70. Serna-Ojeda JC,Nava-Castaneda A. Paralysis of the orbicularis muscle of the eye using botulinum toxin type A in the treatment for dry eye. *Acta ophthalmologica*. 2017;95(2):e132-e37. PMID: 27350144

71. Liu HT,Kuo HC. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology*. 2007;70(3):463-8. PMID: 17905097

72. Waseem Z, Boulias C, Gordon A, et al. Botulinum toxin injections for low-back pain and sciatica. *The Cochrane database of systematic reviews*. 2011(1):CD008257. PMID: 21249702

73. Marras C, Andrews D, Sime E, et al. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. *Neurology*. 2001;56(5):605-10. PMID: 11245710

74. Soares A, Andriolo RB, Atallah AN, et al. Botulinum toxin for myofascial pain syndromes in adults. *The Cochrane database of systematic reviews*. 2014;7:CD007533. PMID: 25062018

75. Nicol AL, Wu, II,Ferrante FM. Botulinum toxin type a injections for cervical and shoulder girdle myofascial pain using an enriched protocol design. *Anesthesia and analgesia*. 2014;118(6):1326-35. PMID: 24842179

76. Garcia-Compean D, Mendoza-Fuerte E, Martinez JA, et al. Endoscopic injection of botulinum toxin in the gastric antrum for the treatment of obesity. Results of a pilot study. *Gastroenterologie clinique et biologique.* 2005;29(8-9):789-91. PMID: 16294147

77. Gui D, Mingrone G, Valenza V, et al. Effect of botulinum toxin antral injection on gastric emptying and weight reduction in obese patients: a pilot study. *Alimentary pharmacology & therapeutics.* 2006;23(5):675-80. PMID: 16480407

78. Foschi D, Corsi F, Lazzaroni M, et al. Treatment of morbid obesity by intraparietogastric administration of botulinum toxin: a randomized, double-blind, controlled study. *International journal of obesity.* 2007;31(4):707-12. PMID: 17006442

79. Babcock MS, Foster L, Pasquina P, et al. Treatment of pain attributed to plantar fasciitis with botulinum toxin a: a short-term, randomized, placebo-controlled, double-blind study. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* 2005;84(9):649-54. PMID: 16141740

80. Diaz-Llopis IV, Rodriguez-Ruiz CM, Mulet-Perry S, et al. Randomized controlled study of the efficacy of the injection of botulinum toxin type A versus corticosteroids in chronic plantar fasciitis: results at one and six months. *Clinical rehabilitation.* 2012;26(7):594-606. PMID: 22144721

81. 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 international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society.* 2013;34(1):8-14. PMID: 23386757

82. Peterlein CD, Funk JF, Holscher A, et al. Is botulinum toxin A effective for the treatment of plantar fasciitis? *The Clinical journal of pain.* 2012;28(6):527-33. PMID: 22673486

83. Wong SM, Hui AC, Tong PY, et al. Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial. *Annals of internal medicine.* 2005;143(11):793-7. PMID: 16330790

84. Hayton MJ, Santini AJ, Hughes PJ, et al. Botulinum toxin injection in the treatment of tennis elbow. A double-blind, randomized, controlled, pilot study. *The Journal of bone and joint surgery American volume.* 2005;87(3):503-7. PMID: 15741614

85. Keizer SB, Rutten HP, Pilot P, et al. Botulinum toxin injection versus surgical treatment for tennis elbow: a randomized pilot study. *Clinical orthopaedics and related research.* 2002(401):125-31. PMID: 12151889

86. Arendt-Nielsen L, Jiang GL, DeGryse R, et al. Intra-articular onabotulinumtoxinA in osteoarthritis knee pain: effect on human mechanistic pain biomarkers and clinical pain. *Scandinavian journal of rheumatology.* 2017;46(4):303-16. PMID: 27733091

87. Kincaid JC,Stewart JD. Focal peripheral neuropathies. *Journal of clinical neuromuscular disease.* 1999;1(2):113. PMID: 19078566

88. Yoon SJ, Ho J, Kang HY, et al. Low-dose botulinum toxin type A for the treatment of refractory piriformis syndrome. *Pharmacotherapy.* 2007;27(5):657-65. PMID: 17461700

89. Breuer B, Sperber K, Wallenstein S, et al. Clinically significant placebo analgesic response in a pilot trial of botulinum B in patients with hand pain and carpal tunnel syndrome. *Pain medicine.* 2006;7(1):16-24. PMID: 16533192

90. Freund BJ,Schwartz M. Relief of tension-type headache symptoms in subjects with temporomandibular disorders treated with botulinum toxin-A. *Headache.* 2002;42(10):1033-7. PMID: 12453036

91. Karacalar A, Yilmaz N, Bilgici A, et al. Botulinum toxin for the treatment of temporomandibular joint disk disfigurement: clinical experience. *The Journal of craniofacial surgery.* 2005;16(3):476-81. PMID: 15915120

92. von Lindern JJ. Type A botulinum toxin in the treatment of chronic facial pain associated with temporo-mandibular dysfunction. *Acta neurologica Belgica.* 2001;101(1):39-41. PMID: 11379274

93. Ziegler CM, Haag C,Muhling J. Treatment of recurrent temporomandibular joint dislocation with intramuscular botulinum toxin injection. *Clinical oral investigations.* 2003;7(1):52-5. PMID: 12673439

94. Lee DH, Jin SP, Cho S, et al. RimabotulinumtoxinB versus OnabotulinumtoxinA in the treatment of masseter hypertrophy: a 24-week double-blind randomized split-face study. *Dermatology.* 2013;226(3):227-32. PMID: 23774030

95. Lee SJ, McCall WD, Jr., Kim YK, et al. Effect of botulinum toxin injection on nocturnal bruxism: a randomized controlled trial. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* 2010;89(1):16-23. PMID: 19855255

96. Shim YJ, Lee MK, Kato T, et al. Effects of botulinum toxin on jaw motor events during sleep in sleep bruxism patients: a polysomnographic evaluation. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* 2014;10(3):291-8. PMID: 24634627

97. Wei J, Xu H, Dong J, et al. Prolonging the duration of masseter muscle reduction by adjusting the masticatory movements after the treatment of masseter muscle hypertrophy with botulinum toxin type a injection. *Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al].* 2015;41 Suppl 1:S101-9. PMID: 25548838

98. Patel AA, Lerner MZ,Blitzer A. IncobotulinumtoxinA Injection for Temporomandibular Joint Disorder. *The Annals of otology, rhinology, and laryngology.* 2017;126(4):328-33. PMID: 28290229

99. 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(11):1523-8. PMID: 11402109

100. Mittal SO, Machado D, Richardson D, et al. Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach. *Mayo Clinic proceedings.* 2017;92(9):1359-67. PMID: 28789780

101. International Headache Society (IHS) [page on the internet]. IHS Classification ICHD-II (revised criteria). . Secondary International Headache Society (IHS) [page on the internet]. IHS Classification ICHD-II (revised criteria). [cited 1/12/2017]. 'Available from:' http://ihs-classification.org/en/02_klassifikation/05_anhang/01.05.01_anhang.html.

Revision History

Revision Date	Revision Summary
12/12/2024	• Clarified coverage criteria for pelvic floor dysfunction to include severe chronic constipation (associated with Hirschsprung's disease) and dyssynergic defecation as functional impairments (no change to policy intent).
12/7/2023	• Added newly approved Daxxify (daxibotulinumtoxinA) to policy. • Simplified chronic migraine criteria for operational consistency. • Updated step therapy for chronic migraines requiring only one step of prior chronic migraine treatment. • Updated reauthorization to 12 months for migraines. • Added updated AAN 2016 guideline statement.
12/9/2022	• Policy criteria language updated for the following (no change to intent): - Congenital aganglionic megacolon (Hirschsprung disease): clarified symptom severity - Migraine headaches: explicitly added oral CGRP antagonist step therapy. - Urinary incontinence, due to detrusor overactivity: added Myrbetriq (mirabegron) as an acceptable step therapy. • Added coverage criteria for refractory postherpetic neuralgia (PHN) after standard of care treatments.
1/20/2021	• Updated COT language. • Added coverage criteria for thoracic outlet syndrome (TOS) in patients with functional impairment. • Updated criteria for hyperhidrosis: - Clarified that secondary infection or skin maceration are considered separate complications. Added inability to satisfy demands of employment as an example of a complication. - Updated step therapy requirements. - Added a requirement that antiperspirant or anticholinergics (topical or oral) have been tried • Clarified initial and continued authorization periods. Re-authorization criteria were aligned for all indications. Re-authorization requires documentation of clinical benefit and up to 4 doses in a 48-week period may be covered. More frequent doses may be covered on a case-by-case basis.
10/28/2020	Clarified migraine criteria, including removal of duplicative criteria.
4/22/2020	• Clarified CGRP monoclonal antibody step therapy for migraines (when used for prophylaxis). CGRPs used as abortive therapy do not meet this criterion.

Revision Date	Revision Summary
	• Added coverage criteria for refractory Raynaud's and pelvic floor dysfunction. • Policy criteria updated for achalasia: simplified coverage to use as part of an endoscopic procedure for upper GI diagnoses.
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • Clarified reauthorization (simplified; no change to intent). • Policy criteria updated for migraine indication to include CGRP monoclonal antibody as step therapy option.
1/31/2019	• Simplified Section I criteria. • Updated investigational uses: - Removed Migraine headache (chronic) in combination with CGRP inhibitors from investigational uses. - Clarified pelvic floor spasm (including pelvic pain, vulvodynia, and vaginismus). • Clarified reauthorization criteria for Section II.
8/17/2018	Added as Investigational uses: Migraine headache (chronic) in combination with CGRP inhibitors.
1/19/2018	• Updated migraine severity criteria to International Headache Society (HIS) standard. • Updated list of Investigational uses (add Dry Eye Disease and OA-related knee pain).
2/17/2017	• The policy criteria were simplified for hyperhidrosis. • Added coverage criteria for congenital aganglionic megacolon (Hirschsprung disease). • Clarified quantity limits to 2 doses per 24-weeks and 4 doses per 48-weeks (versus use of 6 and 12 months, respectively).
2/12/2016	• The policy criteria were updated for hyperhidrosis to clarify the wording regarding medical complications for the definition of medical necessity. • Added coverage criteria for lower limb dystonia, a new FDA-indication. • Added as Investigational uses: dysphagia (non-achalasia), Raynaud's disease, and bruxism/masseter muscle hypertrophy.
1/1/1996	New policy.

Drug names identified in this policy are the trademarks of their respective owners.