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**Medication Policy Manual**

**Policy No:** dru006

**Topic:** Botulinum toxin type A injection:

**Date of Origin:** January 1996

- Botox® (onabotulinumtoxinA)
- Dysport® (abobotulinumtoxinA)
- Xeomin® (incobotulinumtoxinA)

**Committee Approval Date:** February 17, 2017

**Next Review Date:** February 2018

**Effective Date:** March 1, 2017

**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 three commercial botulinum toxin type A products available: Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), and Xeomin (incobotulinumtoxinA). Botulinum toxin type B (rimabotulinum, Myobloc) is covered in a separate policy.

## Policy / Criteria

- I. Most contracts require prior authorization approval of botulinum toxin type A prior to coverage. Botulinum toxin type A may be considered medically necessary when criteria A or B below are met:
- A. **Dystonia or Spastic conditions**, resulting in pain and/or functional impairment, 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
  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. **Torticollis, spasmodic or unspecified**, with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures
  11. **Torsion dystonia** [including both symptomatic (acquired) or idiopathic (primary or genetic; a.k.a. Oppenheim's dystonia)]
  12. **Upper limb spasticity**
- B. **Strabismus**, resulting in vision changes and/or functional impairment
- II. Botulinum toxin A may be considered medically necessary for the diagnoses listed below, when one of the following criteria A through G below is met. There is a diagnosis of:
- 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.

**B. Achalasia/cardiospasm (primary) in patients who:**

1. Have not responded to dilation therapy.

**OR**

2. Are considered poor surgical candidates.

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

**D. Hyperhidrosis (including axillary, palmar and gustatory hyperhidrosis), when BOTH criteria 1 and 2 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, b, or c:

- a. Skin maceration with secondary infection requiring anti-infective treatment (antibiotics or antifungals).

**OR**

- b. Persistent eczematous dermatitis, despite use of topical treatment or systemic anticholinergics.

**OR**

- c. Pain and/or functional impairment due to hyperhidrosis and documentation of inability to perform critical activities of daily living (such as impaired grip and writing ability for employment, or impaired walking).

**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 are not considered to be significant medical complications.

**E. Migraine headache, chronic and severe, when ALL THREE (3) of the criteria in 1, 2, and 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, using the Revised International Headache Society (IHS) criteria for chronic migraine. (*See Appendix 1*)

**AND**

2. There is objective documentation of both criteria a and b below:
  - a. The patient has 15 or more severe headache days per month, based on a headache diary OR chart notes, documenting migraine frequency, severity and characteristics.

**AND**

- b. An evaluation has been performed to assess for rebound headaches caused by medication use [medication overuse headache (MOH)]. A documented plan is in place to address medication overuse, if MOH is identified. Medications that may be associated with rebound headache include, but are not limited to, more than 12 doses per month of narcotics, triptans, caffeine, and NSAIDs.

**AND**

- 3. Documentation that adequate trials of at least **THREE** prophylactic therapies, as specified in criteria a, b, **and** c below were either ineffective, not tolerated, or are contraindicated:
  - a. Topiramate **OR** divalproex sodium (Depakote®).

**AND**

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

**AND**

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

**F. 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 is ineffective or not tolerated.

**G. Sialorrhea** (drooling).

**III. Administration, Quantity Limitations, and Authorization Period**

- A.** Regence Pharmacy Services does not consider botulinum toxin type A to be a self-administered medication.
- B.** For conditions defined in Section I (those resulting in pain and/or functional impairment): When prior authorization is approved, botulinum toxin type A may be authorized in quantities up to 4 injection treatments within a 48-week period. 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.
- C.** For conditions defined in Section II: When prior authorization is approved, botulinum toxin type A may be initially authorized in quantities up to 2 injection treatments within a 24-week period. Documentation of objective clinical response is necessary for continued authorization. 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. Use in excess of 4 doses in a 48-week period is considered not medically necessary.

- IV. Botulinum toxin type A is considered not medically necessary for skin wrinkles or other cosmetic indications.
- V. Botulinum toxin type A 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. Dysphagia (non-achalasia, not otherwise specified)
  - F. Gastroparesis (including diabetic, narcotic-induced, and idiopathic)
  - G. Headache, non-migraine (e.g. chronic daily, tension, cluster)
  - H. Interstitial cystitis
  - I. Low back pain (LBP)
  - J. Medication overuse headache (MOH)
  - K. Motor tic disorder, chronic (including Tics associated with Tourette syndrome)
  - L. Myofascial pain
  - M. Nerve entrapment or compression syndromes, other (those not listed in Section I. above; such as brachial plexus injury, carpal tunnel syndrome Piriformis syndrome, thoracic outlet syndrome)
  - N. Obesity
  - O. Pelvic floor spasm
  - P. Plantar fasciitis pain
  - Q. Raynaud’s disease
  - R. Temporomandibular dysfunction (TMJ), bruxism, and/or masseter muscle spasm.
  - S. Tennis elbow (lateral epicondylitis)
  - T. Tremors [e.g. essential (benign) tremor, Parkinson’s disease-related tremor]
  - U. Upper esophageal sphincter dysfunction associated with neurological disorders

### Position Statement

- There are three botulinum toxin type A products available (abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA) that all work by inhibiting the release of acetylcholine from peripheral cholinergic nerve endings, thereby blocking the cholinergic transmission.
- 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 not 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 exhausted all 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**

#### *Achalasia, primary*

- 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. <sup>[1]</sup>
- Pneumatic dilation is the preferred medical treatment option for primary achalasia. <sup>[2]</sup>
- One Cochrane review concluded that pneumatic dilation produces a higher remission rate at 6 and 12 months compared to botulinum toxin. <sup>[1]</sup>
- There is insufficient evidence to establish efficacy of onabotulinumtoxinA for treatment of dysphagia (non-achalasia). The evidence is limited to one small trial (n=22). Due to the limited amount of studies and a significant amount of heterogeneity in the severity of patients studied, the use of onabotulinumtoxinA for dysphagia is considered investigational. The few human studies done were in very small groups and the results are inconclusive. <sup>[3]</sup>
- There is no evidence to support the use of botulinum toxin for other causes of difficulty swallowing or dysphagia, such as swallowing difficulties associated with neurological disorders, due to upper esophageal sphincter dysfunction. <sup>[4]</sup>

#### *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. <sup>[5]</sup>
  - \* 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. <sup>[6]</sup>

- \*\* A second comparative trial demonstrated a healing rate of 60% with nitroglycerin ointment compared to 96% with onabotulinumtoxinA. [7]
- \*\* 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. [8]
- \*\* A Cochrane review concluded topical CCBs, nitroglycerin and botulinum toxin to be overall similarly effective non-surgical treatment options. However, surgical sphincterectomy remains the most efficacious therapy; however, it is limited by significant risks. [5]
- \* 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. [9]

#### *Congenital aganglionic megacolon (Hirschsprung disease)*<sup>[10-13]</sup>

- 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 or decreased anal sphincter tone. 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, 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. [14]
- 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. [14]
- OnabotulinumtoxinA has not been shown to be effective in the treatment of chronic neck pain without torticollis (with or without cervicogenic headache) and mechanical neck disorders and whiplash. [15,16]

#### *Migraine Headache*

- This policy recognizes the International Headache Society (IHS) Classification of Chronic Migraine Headache for the definition of chronic migraine, which 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. [17]
- Evidence supporting the efficacy of onabotulinumtoxinA in the treatment of migraines has been inconsistent.

- Collective results of seven randomized, controlled episodic migraine trials (totaling more than 1,000 patients) have failed to demonstrate a significant difference between onabotulinumtoxinA and placebo in migraine prevention. Pre-specified primary endpoints and most secondary endpoints were not met. [18-22]
- Two additional trials studying onabotulinumtoxinA in the treatment of chronic migraine were more recently published. [23,24]
  - \* 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) does not support the use of botulinum toxin type A products in the prevention or treatment of headaches. [25] The AAN Technology Assessment of botulinum toxin concludes that:
  - \* They are likely ineffective in treatment of episodic migraine and chronic tension-type headache.
  - \* There is no consistent or strong evidence that they are effective in the treatment of chronic daily 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). [26]

#### Use of Oral Prophylactic Therapies [27,28]

- 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. 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). [27,28]
- There is no evidence that directly compares onabotulinumtoxinA with other prophylactic therapies such as beta-blockers, antiepileptic medications, or tricyclic antidepressants. [29]

#### Other Types of Headache:

- Chronic Daily Headache (CDH): onabotulinumtoxinA has not been shown to be effective in treatment or prevention of CDH. [19,30,31]
- 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. [18,32-35]
  - \* The majority of trials using onabotulinumtoxinA do not support its efficacy in the treatment of tension headaches [32,34-36]

#### *Hyperhidrosis*

- Hyperhidrosis can lead to medical complications, including skin maceration with recurrent bacterial or fungal infection requiring treatment or persistent eczematous dermatitis. [37]
- Palmar hyperhidrosis can interfere with ability to function, when grip is impaired due to hyperhidrosis. [37]
- 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. [37]
- There are several double-blind trials that evaluate onabotulinumtoxinA in patients with primary axillary and primary palmar hyperhidrosis. [29,38,39]
  - \* Treated palms with onabotulinumtoxinA were associated with a 26% reduction in sweating (measured by ninhydrin sweat testing) compared to no reduction with placebo. [38]
  - \* 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. [29]
- The median duration of effect in two pivotal trials that evaluated onabotulinumtoxinA in primary axillary hyperhidrosis was 201 days. [29]
- 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. [40,41]
- 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. [42]

### *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, [43,44] spastic hemiplegia or paraplegia, [45] dysphonia, [29,46], blepharospasm, [47] hemifacial spasm, [48] facial nerve disorders, and demyelinating disease of the CNS, [29,49], as well as a variety of dystonias: hand dystonia, [29] oromandibular dystonia, [29] spasmodic torticollis, [29] and torsion dystonia [29].

### *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). [29,50,51]

### *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. [52-54]
- 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). [55]

## 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. [56]
- 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. [57] The evidence for the use of onabotulinumtoxinA in the treatment of BPH is limited to a variety of Phase II and uncontrolled trials. [29,58]

Additional higher-quality studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition.

#### *Congenital talipes equinovarus (clubfoot) [59]*

- 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. [60] Additional well-controlled studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition.

#### *Gastroparesis (diabetic and idiopathic)*

- 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 [61,62] and others showing no benefit. [63,64]. Additional well-controlled studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition. [29]

#### *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. [29,65]

#### *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. [66] 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. [29]

#### *Motor Tics*

- In one small, poor quality trial, onabotulinumtoxinA reduced tic frequency and urge in patients with Tourette Syndrome or Chronic Tic Disorder. [67] 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. [29,68]

- 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. [69]

### *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. [70,71]
  - \* 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. [72]

### *Orthopedic Pain – Plantar Fasciitis, Lateral epicondylitis (tennis elbow)*

- Four small, exploratory randomized controlled trials reported an improvement in pain scores with onabotulinumtoxinA in patients with plantar fasciitis refractory to other therapies. [73-76]
- Several small, poor quality trials evaluated onabotulinumtoxinA in patients with lateral epicondylitis (tennis elbow). [77-79] Consistent benefit has not been demonstrated across trials.
- Larger, well-controlled trials are needed to establish safety and effectiveness in these conditions and to establish efficacy relative to conventional therapies. [29]

### *Pelvic Floor Spasm*

- There is insufficient evidence to establish efficacy of onabotulinumtoxinA for treatment of pelvic floor muscle spasm. [29]
- A randomized controlled trial (n=60) reported a decrease in pelvic floor muscle pressure with onabotulinumtoxinA in women with pelvic floor spasms. There was no significant difference between onabotulinumtoxinA and placebo for reduction in pain scores. [80]

### *Nerve Entrapment and Compression Syndromes (such as Brachial Plexus Injury, Carpal Tunnel Syndrome, Piriformis Syndrome, Thoracic outlet syndrome)*

- Piriformis syndrome is a form of myofascial pain characterized by sciatica and buttock tenderness.
  - \* Few case reports describe the management of piriformis syndrome. [81] 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. [29,82]
- There is insufficient evidence to establish efficacy of botulinum toxin for treatment of carpal tunnel syndrome. The evidence is limited to one pilot trial. [83]
- 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. 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. [84]
- \* Strengthening exercises, physical therapy and surgery are the standard of care. [85]

#### *Raynaud's Disease*

- There is insufficient evidence to establish efficacy of onabotulinumtoxinA for treatment of Raynaud's syndrome. The evidence is limited to one pilot trial and one retrospective case series. [86,87]

#### *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. [88-91]
- Several small, poor quality trials evaluated onabotulinumtoxinA in patients with bruxism, masseter muscle spasm, and/or masseter hypertrophy. Consistent benefit has not been demonstrated across trials. Additional larger trials are needed to establish the safety and efficacy of onabotulinumtoxinA. [92-95]

#### *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. [29,96]
- OnabotulinumtoxinA resulted in significant improvement of postural, but not kinetic essential hand tremors; however, there is not compelling evidence that onabotulinumtoxinA leads to better functional efficacy for patients. [96]

#### **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. [49]
- 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 <sup>[97]</sup>**

- 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 or 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
Botulinum Toxin, Blue Cross BlueShield Association Medical Policy, 5.01.05. Review Date: 12/2016.
Treatment of Hyperhidrosis, BlueCross BlueShield Association Medical Policy 8.01.19. Review Date: 5/2016.
Surgical Treatments for Hyperhidrosis, Medical Policy; Med 165.
Myobloc®, rimabotulinumtoxinB, Medication Policy Manual, Policy dru045
Cosmetic and Reconstructive Surgery, Surgery Section; Medical Policy No. 12.

Codes	Number	Description
HCPCS	J0585	Injection, onabotulinumtoxinA, 1 unit
HCPCS	J0586	Injection, abobotulinumtoxinA, 5 units
HCPCS	J0588	Injection, incobotulinumtoxinA, 1 unit

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### Revision History

Revision Date	Revision Summary
02/17/2017	<ul style="list-style-type: none"> <li>- The policy criteria were simplified for hyperhidrosis.</li> <li>- Add coverage criteria for congenital aganglionic megacolon (Hirschsprung disease).</li> <li>- Clarify quantity limits to 2 doses per 24-weeks and 4 doses per 48-weeks (versus use of 6 and 12 months, respectively).</li> </ul>
2/12/2016	<ul style="list-style-type: none"> <li>- The policy criteria were updated for hyperhidrosis to clarify the wording regarding medical complications for the definition of medical necessity.</li> <li>- Add coverage criteria for lower limb dystonia, a new FDA-indication.</li> <li>- Added as Investigational uses: dysphagia (non-achalasia), Raynaud's disease, and bruxism/masseter muscle hypertrophy.</li> </ul>