BENEFIT DESCRIPTION AND LIMITATIONS OF COVERAGE

ITEM: Botox® (onabotulinumtoxinA, injection)
PRODUCT LINES: Commercial HMO/PPO/CDHP
COVERED UNDER: HMO: Medical
PPO/CDHP: Medical
DESCRIPTION: OnabotulinumtoxinA (previously known as botulinum toxin type A) is a neurotoxin produced by Clostridium botulinum, spore-forming anaerobic bacillus, which appears to affect only the presynaptic membrane of the neuromuscular junction in humans, where it prevents calcium-dependent release of acetylcholine and produces a state of denervation. Muscle inactivation persists until new fibrils grow from the nerve and form junction plates on new areas of the muscle-cell walls. Intradermal injection results in temporary sweat gland denervation, reducing local sweating.

CPT/HCPCS Code: J0585
Company Supplying: Allergan Pharmaceuticals
Setting: Intramuscular
Coverage Criteria: Express Scripts, Inc. monograph dated 03/19/2010
Approval Period: Professional judgment based on indication

Recommended Authorization Criteria

Botulinum toxin type A has been used to treat numerous medical conditions. The risk versus benefits should be carefully evaluated before therapy is initiated, as efficacy and safety may not be established in all of these conditions. Coverage of botulinum toxin type A is recommended for non-cosmetic, medical conditions. The following list of medical indications gives examples for which coverage of botulinum toxin type A is recommended. This is not an all-inclusive list. Requests for botulinum toxin type A for indications not included in the following list will be evaluated by a pharmacist and/or a physician on a case-by-case basis to determine a coverage recommendation for the client.

FDA-Approved Indications

1. Blepharospasm or strabismus associated with dystonia. Botox is FDA-approved for this indication.

2. Cervical dystonia (torticollis). Botox is FDA-approved for this indication. Note: Cervical dystonia is also known as spasmodic or cervical torticollis.
3. **Primary axillary hyperhidrosis.** Approve after a trial with at least one topical agent. Botox is FDA-approved for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. Topical antiperspirants (e.g., topical aluminum chloride) are the recommended first-line therapy for the treatment of primary axillary hyperhidrosis.

4. **Upper limb spasticity to decrease tone in elbow flexors, wrist flexors and finger flexors.** Botox is FDA-approved for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis). For spasticity that does not fit this criterion see Other Uses with Supportive Evidence Spasticity.

**Other Uses with Supportive Evidence**

1. **Achalasia (lower esophageal sphincter dysfunction).** The clinical data on the use of botulinum toxin A for treatment of achalasia are extensive and suggest that it is effective in the majority of patients treated; 70% to 100% of patients experience short-term symptomatic relief. A large amount of data from both uncontrolled studies and randomized, controlled studies support the effectiveness of botulinum toxin A as a non-invasive therapeutic alternative. It is particularly useful in patients with vigorous achalasial variant, poor surgical candidates, and in situations where it can be used as a diagnostic tool. Other small (mean sample size n = 34 patients), randomized, double-blind, placebo-controlled trials results show botulinum toxin A as more effective than placebo but associated with shorter duration of relief compared with pneumatic dilation or surgical intervention. Botulinum toxin A may be an alternative treatment for patients who are not candidates or do not desire pneumatic dilation or surgery.

2. **Anal Fissure (anal sphincter).** There is an extensive amount of data from open-label studies, randomized, placebo-controlled trials, and randomized, comparative trials supporting the efficacy of botulinum toxin A in the treatment of anal fissures. The majority of the available data are evaluating use of Botox (n = 858). Overall, single injections of botulinum toxin A have resulted in healing of 60% to 82% of anal fissures. Botulinum toxin A appears to be a safe and effective short-term treatment of chronic anal fissure, demonstrating a healing rate of 70% - 98% after two to four months. Botox has been shown to be more effective than topical nitroglycerin but less effective than surgery in inducing and maintaining fissure healing.

3. **Benign prostatic hyperplasia (BPH).** Approve after a trial with at least two other therapies (e.g., alpha₁-blocker, 5 alpha-reductase inhibitor, transurethral resection of the prostate [TURP], transurethral microwave heat treatment, transurethral needle ablation [TUNA®], interstitial laser therapy, stents, various forms of surgery). In one 12-month, randomized, double-blind, placebo-controlled study in 30 men with moderate to severe symptoms of urinary obstruction as a result of BPH, Botox significantly decreased symptom scores, prostate-specific antigen (PSA) concentrations, prostate volume, and post void residual urine volume from baseline compared to placebo. Significantly more patients treated with botulinum toxin A reported subjective symptomatic relief compared to those treated with placebo. This study did not
specify previously tried therapies. Similar results were seen in one small, prospective, open-label study in 10 men with BPH who were poor surgical candidates. Another study involving 41 men with symptomatic BPH refractory to medical treatment, 75.6% of patients experienced a ≥ 30% improvement in lower urinary tract symptom and quality-of-life indices. Other small studies show improvement after 1 month of the transperineal or intraprostatic Botox injection with sustained treatment response for 6 to 8 months.

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

5. **Chronic low back pain (LBP).** Approve after a trial with at least two other pharmacologic therapies (e.g., nonsteroidal anti-inflammatories, antispasmodics, muscle relaxants, opioids, antidepressants) and if being used as part of a multimodal therapeutic pain management program. In one 8-week, randomized, double-blind, placebo-controlled trial in 31 patients with chronic low back pain (no causative factor identified in the majority of patients, 6 due to a history of disc disease, 3 due to discectomy, and 4 due to trauma), Botox in addition to their current pharmacologic treatment regimen resulted in significantly greater improvement in pain relief and degree of disability compared to placebo. Short-term retrospective studies also suggest benefit from this form of treatment in chronic LBP. A 14-month, open-label, prospective study evaluated the short-term and long-term effects of paraspinal muscle injections of Botox in 75 patients with refractory chronic LBP. At 3 weeks, 53% and at 2 months, 52% reported significant pain relief.

6. **Plantar fasciitis.** In one randomized, double-blind, placebo-controlled study in 27 patients with plantar fasciitis refractory to more conventional treatment strategies (undefined), Botox was significantly more effective than placebo in providing pain relief and improving overall foot function at both 3 and 8 weeks after treatment.

7. **Tinnitus.** Approve after a trial with at least two other pharmacologic therapies (e.g., lidocaine, antihistamines, antidepressants, anxiolytics, diuretics, anticonvulsants, antispastics) and tinnitus retraining therapy and being prescribed by an ENT (i.e., otolaryngologist – head and neck surgery). Currently available oral agents have been tried with variable results and have been limited in their ability to successfully control tinnitus long-term. Tinnitus retraining therapy may be considered the most successful treatment available to date. In one 4-month, randomized, double-blind, placebo-controlled study in 30 patients with tinnitus (unilateral or bilateral sensorineural hearing loss, Meniere’s disease-associated tinnitus, or mixed hearing loss) [16 of the 30 patients were refractory to other pharmacologic therapies], Botox resulted in significant subjective improvement in 7 patients compared to placebo and a significant decrease in tinnitus handicap inventory scores compared to baseline.

8. **Headache** (e.g., migraine, chronic tension headache, cervicogenic [‘whiplash’] headache, chronic daily headache). Approve after a trial with at least two other pharmacologic therapies and prescribed by or after consultation with a neurologist or headache specialist. Several
retrospective reviews, prospective open-label studies, and a few randomized, double-blind, placebo-controlled trials have shown botulinum toxin A to be effective according to several outcome measures as preventative therapy for episodic and chronic migraine, chronic daily headache of varying forms, and chronic tension headache. Botox was effective in the treatment of cervicogenic headache in one randomized, double-blind, placebo-controlled trial. Several other placebo-controlled studies involving a total over 300 patients show conflicting results that Botox is no more effective than placebo in reducing migraine frequency or reducing the average number of days with headache, analgesic use, or improving duration of sleep in patients with chronic tension-type headaches. According to the National Headache Foundation’s standards of care guidelines, botulinum toxin A is considered a therapeutic option in the prophylaxis of migraine headache; it is categorized with several other medications as an agent demonstrating lower efficacy with limited strength of evidence and is further classified as a special-use therapy. Less commonly used treatment modalities used for chronic daily headache, which includes botulinum toxin A, are best used by headache specialists.

9. **Palmar/plantar hyperhidrosis and facial hyperhidrosis.** Approve after a trial with at least one topical agent (e.g., aluminum chloride). Overall, topical antiperspirants (e.g., aluminum chloride) are the recommended first-line therapy for the treatment of primary focal hyperhidrosis, other conventional treatments include oral anticholinergics; topical treatment is more effective in mild cases compared to more severe cases. The efficacy of Botox is well established in the treatment of primary focal/palmar hyperhidrosis based on data from both randomized, double-blind, placebo-controlled studies and open-label studies.

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

11. **Salivary hypersecretion.** Botulinum toxin A has been studied in the treatment of sialorrhea associated with Parkinson’s Disease, parkinsonian syndromes, cerebral palsy, head and neck carcinoma, neurodegenerative disease, stroke, and amyotrophic lateral sclerosis (ALS). Most of the data comes from open-label studies with small groups of patients (using Botox or Dysport). Overall, up to two-thirds of patients in these studies experienced moderate or marked improvement. An open-label, non-blinded, prospective study in 20 children with cerebral palsy and relative sialorrhea showed significant improvement in sialorrhea and quality of life scores after botulinum toxin A injections at 4 and 12 weeks.

12. **Spasticity (i.e., spasticity or hypertonia due to cerebral palsy, stroke, brain injury, spinal cord injury, multiple sclerosis, hemifacial spasm).** Botulinum toxin is the most widely used treatment for focal spasticity. Neurosurgery and oral medications have a long history in spasticity treatment.
baclofen, benzodiazepines, phenytoin, or gabapentin) yet they have dose-limiting side effects and limited diffusion across the blood brain barrier. Several randomized, double-blind, placebo-controlled trials support the effectiveness of botulinum toxin A in the treatment of focal spasticity/focal hypertonia. For lower limb spasticity, four randomized controlled trials in > 100 patients treated with botulinum toxin A had significant improvement in Ashworth scores or improved muscle tone. In both upper and lower limb spasticity, studies have shown modest improvement of active limb function in a select subgroup of patients. Other randomized, controlled trials evaluated botulinum toxin A for the management of upper limb spasticity in children with cerebral palsy and showed significant improvement in spasticity/tone, range of motion, and functional gains after botulinum toxin A injections. The majority of the data is evaluating the use of Botox. Treatment with botulinum toxin A in hemifacial spasm appears to remain effective over long-term use of several years (4 to 10 years) most cases do not require a dosage increase.

13. Essential tremor. **Approve after a trial with at least one other pharmacologic therapy** (e.g., primidone, propranolol, benzodiazepines, gabapentin, topiramate). Propranolol and primidone are first-line therapy in the treatment of essential tremor. Botulinum toxin A is considered a second-line medication option along with benzodiazepines, gabapentin, and topirimate. Botox was shown to significantly improve tremor severity and postural tremor outcomes compared to placebo in two randomized, double-blind, placebo-controlled studies in a total of 158 patients with moderate to severe essential hand tremor. Open-label studies as well as one double-blind, placebo-controlled study support the effectiveness of botulinum toxin A in improving essential voice tremor and essential head tremor (head tremor without dystonia).

14. Dystonia, other than cervical (e.g., focal dystonias, tardive dystonia, anismus). In one large, prospective, 5-year, open-label study in 477 patients with various focal dystonias symptomatic despite optimum pharmacological or surgical therapy, 93% of patients reported moderate to marked relief of their spasm after treatment with Botox. Data from several other smaller open-label studies, case reports, and small, randomized, controlled trials further support the effectiveness of Botox in the treatment of non-cervical dystonias. Botulinum toxin A is the most widely accepted treatment for spasmodic dysphonia, a focal laryngeal dystonia, viewed as the treatment of choice by the American Academy of Otolaryngology-Head and Neck Surgery.

15. Bladder/Voiding/Urethral dysfunction. **Approve after a trial with at least one other pharmacologic therapy.** Oral pharmacologic therapy with antimuscarinic agents is the first-line treatment of overactive bladder/detrusor hyperreflexia. A large amount of data from retrospective reviews, open-label studies, and controlled trials (non-randomized) support the efficacy of Botox in the treatment of neurogenic (e.g., spinal cord injury and multiple sclerosis) lower urinary tract dysfunction. One of the largest clinical series is a multicenter, retrospective study in 200 patients with neurogenic bladder treated with Botox; the 3- and 9-month follow-up, urodynamic testing showed significant and durable increases in maximum bladder capacity and decreases in voiding pressure. Data from several small, open-label studies support the efficacy and safety of Botox in the treatment of non-neurogenic lower urinary tract dysfunction (Overactive Bladder) resistant to conventional therapy, as evidenced by increased functional bladder capacity and decreased urge incontinence post-
treatment. The use of Botox for non-neurogenic overactive bladder in children (n = 21) who are resistant to common treatments has been shown to be a safe and effective treatment.

16. **Gastroparesis. Approve after a trial with at least one promotility drug (e.g., metoclopramide, tegaserod, erythromycin).** In four open-label studies ranging in size from 3 to 20 patients with idiopathic, diabetic, or postsurgical gastroparesis, Botox was effective in increasing gastric emptying of a solid meal and improving symptoms for up to 30 weeks.

17. **Frey’s syndrome (gustatory sweating).** Botulinum toxin A has been shown to be highly effective in treating the symptoms (i.e., hyperhidrosis and facial flushing) of Frey’s syndrome and has emerged as the treatment of choice in the treatment of this condition. In six open-label trials in a total of 132 patients with Frey’s syndrome/gustatory sweating, injections of Botox resulted in the complete absence or pronounced improvement of symptoms in all patients studied.

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

19. **Speech/voice disorder (e.g., dysphonias).** Botulinum toxin A is currently the standard of care for the symptomatic management of spasmodic dysphonia. Several prospective, open-label studies support the effectiveness of Botox in improving tracheoesophageal speech failure, ventricular dysphonia, and voice tremor.

20. **Tourette’s syndrome. Approve after a trial with at least one more commonly used pharmacologic therapy (e.g., neuroleptics, clonidine, selective serotonin reuptake inhibitors, psychostimulants).** In one prospective, open-label study in patients refractory to conventional therapy, 35/186 (19%) of patients who received Botox experienced complete control of their motor tics, with less improvement seen on vocal tics (no statistical analysis). In another prospective, open-label study in 30 patients refractory to conventional therapy, treatment with Botox improved vocal tics in 93% of patients, with 50% being tic-free.

21. Other indications: review with the pharmacist

No exceptions are recommended for the Botox Cosmetic formulation of botulinum toxin type A.

**Exclusions**

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

2. **Allergic rhinitis.** One 8-week, randomized, double-blind, placebo-controlled study in 34 patients with allergic rhinitis showed that treatment with botulinum toxin A resulted in significantly improved symptom scores (i.e., rhinorrhea, nasal obstruction, and sneezing) at all time points and a significantly lower total symptom score at study end compared to placebo. Patients were advised not to take any additional allergy therapy. The study did not specify which allergy medications patients had tried prior to study enrollment. Botulinum toxin A has not been compared to any other medications used to treat allergic rhinitis. The American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma, and Immunology (JCAAI) joint practice parameter for management of rhinitis does not mention botulinum toxin A as a treatment option, even in patients refractory to the more standard therapeutic regimens. Allergic rhinitis is a common condition with an armamentarium of well-established pharmacologic options and combinations thereof. More data are needed to define Botox’s place in therapy in the treatment of allergic rhinitis.

3. **Gait freezing in Parkinson’s disease (PD).** A non-blinded, pilot study in 10 patients with PD in whom freezing of gait (FOG) was the predominant and disabling symptom showed varying degrees of improvement of FOG severity after treatment with botulinum toxin type A. In another study, 12 subjects with PD and FOG were studied in a crossover design which showed no difference between botulinum toxin type A and placebo. A third double blind, placebo-controlled study in 11 patients with advanced PD and disabling FOG failed to show any benefit with botulinum toxin A compared to placebo and was terminated early due to increased fall risk among the botulinum toxin type A treated group.

4. **Vaginismus.** In one small (n = 13), placebo-controlled study, all patients treated with Botox (n = 8) improved. More data are needed to define the place in therapy of Botox in the treatment of vaginismus.

5. **Dysphagia** (upper esophageal sphincter dysfunction). Botulinum toxin A has been used to successfully treat cricopharyngeal dysfunction, which is often the source of dysphagia. In one small (N = 12), open-label study Botox significantly improved radiographic and patient ratings compared to baseline. Successful results have also been achieved in one case series. More data are needed to define the place in therapy of Botox in the treatment of dysphagia.

6. **Interstitial cystitis.** In one open-label study in 13 patients with refractory interstitial cystitis, treatment with botulinum toxin A (Botox or Dysport) resulted in significant improvement from baseline in urinary tract symptoms, urodynamic measures, and pain scores. More data are needed to define the place in therapy of Botox in the treatment of interstitial cystitis.

7. **Crocodile tears syndrome** (gustatory epiphora/gustatory lacrimation). In one prospective, open-label study 2 patients with Crocodile tears syndrome (and 9 patients with Frey’s syndrome) were successfully treated with Botox.
Similar results have been achieved in several case reports and case series. Crocodile tears is an unusual phenomenon and is rarely severe enough to require treatment. Invasive treatments have been tried with controversial results. More data with Botox are needed.

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

Coverage of Botox® Cosmetic is not recommended.

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