**Botulinum Toxin**

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**Replaces** 5.01.05

**Policy**

**Note:** As experience has been gained, medical consensus has gradually developed that individual botulinum toxin products have similar, but not identical, properties. As a result, FDA-approved indications for the toxins differ. The Company has combined the indications for the different botulinum toxin products into the single list below. The Company will consider any of the botulinum toxin products medically necessary when they meet the following criteria; however, **it is the responsibility of the provider to use each product in accordance with FDA-approved or compendia-supported indications in accordance with their medical judgment.**

The use of botulinum toxin may be considered **medically necessary** for the following indications:

- Strabismus;
- Blepharospasm, facial nerve (VII) disorders;
- Upper limb spasticity;
- Chronic migraine or tension-type headaches in patients who are refractory to preventive measures and have failed or cannot take headache aborting medications;
- Trigeminal neuralgia (cranial nerve V);
- Cervical dystonia (spasmodic torticollis) whether congenital, due to childbirth injury, or trauma;
- Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates;
- Chronic anal fissure;
- Urinary incontinence caused by neurogenic or idiopathic overactive detrusor in patients who are refractory to anticholinergic agents;
- Piriformis syndrome; and
- Sialorrhea.

The use of botulinum toxin may be considered **medically necessary** for the treatment of dystonia resulting in functional impairment (interference with joint function or mobility) and/or pain in patients with any of the following hereditary, degenerative, or demyelinating diseases of the central nervous system:

**Focal dystonias**

- Organic writer's cramp (occupational dystonia);
- Oromandibular dystonia (orofacial dyskinesia, Meige syndrome);
- Symptomatic torsion dystonia;
- Laryngeal spasm (spastic dysphonia); and
• Idiopathic torsion dystonia.

**Spastic conditions**
• Hereditary spastic paraplegia;
• Neuromyelitis optica;
• Schilder’s disease;
• Lower limb spastic hemiplegia;
• Lower limb spasticity related to stroke; or
• Infantile cerebral palsy.

The use of botulinum toxin is considered **cosmetic** as a treatment of wrinkles or any other cosmetic indications.

The use of botulinum toxin is considered **investigational** for other indications, including but not limited to:
• Chronic low back pain,
• Myofascial pain syndrome,
• Cluster headache or tremors such as benign essential tremor, and
• Chronic motor tic disorder (ICD-9 307.22) and tics associated with Tourette syndrome (ICD-9 307.23).

**Note:** Botulinum toxin as a treatment of hyperhidrosis is considered in a separate medical policy. (See Related Policies)

**Related Policies**

| 8.01.519 | Treatment of Hyperhidrosis |

**Policy Guidelines**

N/A

**Description**

Botulinum is a family of toxins produced by the anaerobic organism *Clostridium botulinum*. There are seven known serotypes of botulinum toxin: types A, B, C-1, D, E, F, and G. When administered intramuscularly, all botulinum toxins reduce muscle tone by interfering with the release of acetylcholine from nerve endings.

Three distinct serotype A botulinum toxin products, Botox® (onabotulinumtoxinA), Xeomin® (incobotulinumtoxinA), and Dysport® (abobotulinumtoxinA), and one serotype B botulinum toxin product, Myobloc® (rimabotulinumtoxinB), have been approved by the U.S. Food and Drug Administration (FDA). Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each botulinum toxin product and cannot be compared or converted into units of another product, i.e., one unit of Botox is not equal to one unit of Dysport, one unit of Xeomin, or one unit of Myobloc. In addition, there are no universally accepted safe dose conversion ratios. Failure to recognize the unique characteristics of each formulation may lead to undesired patient outcomes.

*Botox (onabotulinumtoxinA):* The FDA-approved label for Botox states that it is indicated for the treatment of adults with cervical dystonia, upper limb spasticity, and for the prophylaxis of headaches in adult patients with chronic migraine (at least 15 headache days per month with headache lasting 4 hours a day or longer). Botox is also indicated in patients greater than 12 years old for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders.
Dysport (abobotulinumtoxinA): The FDA-approved label for Dysport states that it is indicated for the treatment of adults with cervical dystonia.

Xeomin (incobotulinumtoxinA): The FDA-approved label for Xeomin states that it is indicated for the treatment of adults with cervical dystonia or blepharospasm previously treated with Botox (onabotulinumtoxinA).

Myobloc (rimabotulinumtoxinB): The FDA-approved label for Myobloc states that it is indicated for the treatment of cervical dystonia to reduce the severity of abnormal head position and neck pain.

Dystonia is a general term describing a state of abnormal or disordered tonicity of muscle. As an example, achalasia is a dystonia of the lower esophageal sphincter, while cervical dystonia is also known as torticollis. Spasticity is a subset of dystonia, describing a velocity-dependent increase in tonic-stretch reflexes with exaggerated tendon jerks. Spasticity typically is associated with injuries to the central nervous system. Spasticity is a common feature of cerebral palsy. Since its FDA approval in 1989, Botox has been used for a wide variety of off-label indications associated with dystonia, ranging from achalasia and cerebral palsy to anal fissures. In addition to widening indications, Botox has also been used in children under 12, particularly for the treatment of cerebral palsy.

Note: Botulinum toxin as a treatment of hyperhidrosis is considered separately in another medical policy. (See Related Policies)

Scope

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply.

Benefit Application

Electromyographic (EMG) guidance may be used to direct the injection of the botulinum toxin, particularly if the larynx or esophagus is being treated. If so, EMG guidance is considered an integral part of the procedure and no additional reimbursement for the EMG is warranted. Injection of the vocal cords is done in association with laryngoscopic guidance. As indicated by the CPT codes (31513, 31570, or 31571), the laryngoscopy is considered an integral part of the procedure and separate billing for the laryngoscopy and injection is not warranted.

Botulinum toxin as a treatment of achalasia requires a separate endoscopy procedure, which is billed separately.

Botulinum toxin is covered under the Medical benefit since it is not self-administered.

For the purposes of this policy, the following definitions apply:

**Cosmetic:** Cosmetic services are those which are primarily intended to preserve or improve appearance. Cosmetic surgery is performed to reshape *structures* of the body in order to improve the patient's appearance or self-esteem.

**Physical functional impairment:** In this policy, functional impairment means a limitation from normal (or baseline level) of physical functioning that may include, but is not limited to, problems with ambulation, mobilization, communication, respiration, eating, swallowing, vision, facial expression, skin integrity, distortion of nearby body parts or obstruction of an orifice. The physical functional impairment can be due to structure, congenital deformity, pain, or other causes. Physical functional impairment excludes social, emotional and psychological impairments or potential impairments.
Reconstructive surgery: In this policy, reconstructive surgery refers to surgeries performed on abnormal structures of the body, caused by congenital defects, developmental abnormalities, trauma, infection, tumors or disease. It is generally performed to improve function.

Rationale

The original policy focused on onabotulinumtoxinA (Botox) only and was based both on the results of a series of randomized placebo-controlled clinical trials and a 1996 TEC assessment that focused on the use of botulinum toxin in the treatment of spasticity. The current policy is based on additional literature published since 1997. The literature review focuses on randomized placebo-controlled clinical trials. While the bulk of the literature is based on trials using onabotulinumtoxinA (Botox), it is anticipated that other botulinum toxin serotype A products and the botulinum toxin serotype B (Myobloc) may be used for the same range of off-label indications as onabotulinumtoxinA. However, it is expected that providers will use these products in accordance with FDA-approved or compendia-supported indications unless there are valid and documented reasons stating why the unapproved or unsupported product is used.

Achalasia

Achalasia is a primary esophageal motor disorder characterized by abnormal lower esophageal sphincter relaxation. While prior randomized controlled trials validated the efficacy of botulinum toxin in treating achalasia, until recently there was no randomized trial comparing botulinum toxin with pneumatic dilation, perhaps considered the gold standard non-surgical treatment. In 1999, Vazzi and colleagues reported on a trial that randomized 42 patients with achalasia to receive either botulinum toxin or undergo pneumatic dilation. Pneumatic dilation results in a significantly higher cumulative remission rate. At 12 months, 70% of patients in the dilation group were still in remission, compared to 32% of those in the botulinum toxin group. These results reflect the fact that the effects of botulinum toxin are known to be reversible, but also the fact that pneumatic dilation can provide durable treatment effects. The authors conclude that while botulinum toxin is an effective therapy, pneumatic dilation is the preferred medical treatment option.

Myofascial Pain Syndrome

Painful muscles with increased tone and stiffness containing trigger points characterize myofascial pain syndrome. Patients are often treated with injections of the trigger points with saline, dilute anesthetics, or dry needling. These trigger point injections, while considered established therapy, have been controversial since it is unclear whether any treatment effect is due to the injection, dry needling of the trigger point, or a placebo effect. Wheeler and colleagues conducted a randomized trial of 33 patients with myofascial pain syndrome who were randomized into 3 groups; one group receiving 50 units of botulinum toxin, one group receiving 100 units of botulinum toxin, and one group receiving normal saline. All 3 groups showed similarly significant treatment effects, based on the Neck Pain and Disability Visual Analogue Scale. When looking separately at the 9 patients who had two injections of botulinum compared to the 4 patients who had an injection of 100 units of botulinum following a placebo injection, the authors found improved pain relief. However, due to the small numbers who underwent a second injection, the difference was not clinically significant. The author suggests that further investigation using higher doses of botulinum and sequential injections are needed.

Spasticity Related to Stroke

Spasticity related to stroke may be a significant functional problem. Plantar flexion spasticity may impede walking. Peripheral neurolysis with phenol injections has been used for many years, but recently botulinum toxin injections have been investigated. Kirazli and colleagues compared the effects of phenol block and botulinum toxin in a randomized trial of 20 patients with spastic foot after stroke. The authors reported that both injections were associated with significant improvements, with botulinum toxin outperforming phenol injections after the first month of treatment, with equal treatment effects at 2 and 3 months. Possible advantage of the botulinum toxin is the relative ease of the procedure (15 to 30 minutes), while phenol injection may take up to 2 hours to target motor nerve for injection. Smith and colleagues investigated the use of botulinum toxin in a trial that randomized 21 patients with upper limb spasticity related to stroke or head injury. There was a significant reduction in spasticity in the wrist and fingers in the botulinum group. The effects were transitory and disappeared at 12
weeks.

**Anal Fissure**

Chronic anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter, and is treated surgically with an internal sphincterectomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin represented a logical medical approach. Maria and colleagues reported on a study that randomized 30 patients with chronic anal fissure to receive either 2 injections of 20 units of botulinum toxin, on either side of the fissure, or 2 injections of saline. After 2 months, 11 patients in the treatment group reported healing, compared to only 2 in the control group. The 4 patients who still had fissures after 2 months underwent retreatment with botulinum toxin; 2 of these 4 patients reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80%. Nitroglycerin ointment has also been used successfully to treat anal fissure. Recently Brisinda and colleagues compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group.

**Tremor**

Tremor may be defined as alternate or synchronous contractions of antagonistic muscles. Some patients may be disabled by severe or task-specific tremors. Tremors are also a frequent component of dystonias, and successful treatment of dystonias resulted in an improvement in tremors. Botulinum toxin has been investigated in patients with tremors unrelated to dystonias. One randomized study has been reported of 10 patients with essential head tremor. Patients were randomized to receive botulinum injections into the sternocleidomastoid and splenius capitis muscles. Five patients improved in the treatment group compared to 3 in the control group. The lack of statistical significance may be related to the small size of the study.

**Migraine**

The interest in using botulinum as a treatment of migraine stemmed from the observation that patients receiving pericranial injections of botulinum toxin for other reasons reported a decrease in the incidence of migraine. While it may exert its effect by relieving the muscle tension associated with migraine, others have proposed an independent action. Ward reported on a trial of pericranial injections of botulinum toxin as a prophylactic treatment of migraine. A total of 123 patients were randomized to receive either placebo injections, or 25 U or 75 U of botulinum toxin. The patients were followed for 3 months after the injections, during which time they kept a headache diary. A significantly greater proportion of patients receiving 25 U of botulinum (but not 75 U) reported a decrease of two or more migraines.

Blumenfeld conducted a retrospective chart review of 271 patients diagnosed with episodic migraine, tension type headache, chronic daily headache and mixed type headache. Of the patients surveyed, 85.6% reported improvement in headache frequency and severity, and 95% tolerated the medication without side effects. Currently, four randomized controlled trials are being conducted in patients with migraine and other types of headache.

Silberstein et al. enrolled 123 patients with migraine (diagnosis according to IHS criteria) with two to eight attacks per month. The study was randomized, double blind and placebo-controlled. The patients were treated with 25 U or 75 U BotoxH against placebo. The follow-up control revealed a significant reduction of migraine frequency in month 3 and of pain intensity in months 2 and 3 in the 25 U group compared with placebo. Significantly more patients in the 25 U group had a reduction of >50% in month 3 compared with the control group. However, the patients treated with 75 U showed no significant results.

Brin et al. were able to show a significant reduction of pain intensity but not of migraine frequency. The study was randomized, double-blind, and placebo-controlled, but the differentiation of 56 patients into four subgroups, the unknown diagnosis criteria, and the unknown dose of botulinum toxin A do not support a classification better than grade 2 evidence. Binder et al., and Mauskop and Basdeo studied botox in migraine patients in small uncontrolled studies.

See “2010 Update” at the end of this section of the policy for discussion of the evidence supporting approval of onabotulinumtoxinA (Botox) for the treatment of chronic migraine.
Tension Headache
Rollnik and colleagues reported on a double blind placebo controlled trial of botulinum A toxin in the treatment of tension headache. The study included 21 subjects who were randomized to receive either pericranial injections of botulinum A or placebo. At evaluations at 4, 8, and 12 weeks, no significant difference in outcome between the treatment and placebo group was identified. Another randomized trial of 37 patients with tension headaches reported that botulinum treatment was associated with an improvement in headache intensity. However, at baseline, the number of headache-free days was greater in the group randomized to receive botulinum treatment, limiting interpretation. Based upon expert opinion presented at the January 2004 Premera Pharmacy & Therapeutics Committee, it was decided that chronic, tension-type headaches could receive some improvement from the administration of botulinum toxin.

Cervicogenic Headache
Freund and colleagues reported on a placebo-controlled trial that randomized 26 patients with chronic headache related to whiplash injury to receive either botulinum toxin or placebo injections. Although the treatment group reported a significant improvement in pain while the placebo group reported no improvement, the study design was flawed in that at baseline less pain was reported by the placebo group.

Other Reported Indications without Randomized Controlled Trials
Several small case series have reported promising results in patients with excessive drooling, which may be associated with Parkinson disease. Refractory headaches, which may be associated with chronic daily headaches or migraines, may be associated with increased muscle tension of the pericranial muscles. Wheeler reported on a case series of 4 patients with daily headaches and identifiable areas of increased muscle tension. The author reported that the patients reported decreased frequency and severity of headaches. This finding must be confirmed by larger controlled studies.

2002 Update
This policy is updated with a 2002 TEC Assessment that focused on botulinum toxin as a treatment of low back pain. The TEC Assessment concluded that there was insufficient evidence to permit scientific conclusions regarding the indication; therefore, the policy statement is unchanged. Specifically, the TEC Assessment offered the following observations and conclusions:

- Regarding tension headaches, the TEC Assessment focused on the randomized trials of Rollnik, Smuts, and Schmitt. Only the Smuts trial reported a significant effect of botulinum toxin. The TEC Assessment concluded that these small and conflicting trials represented insufficient evidence to draw significant conclusions.
- The Assessment did not identify any studies of botulinum toxin as a technique to prevent cluster headaches.

Chronic Low Back Pain
The literature search revealed a single study using botulinum toxin A in patients with low back pain. Foster et al. report a randomized, double-blind study of botulinum toxin A in 31 consecutive patients with chronic low back pain. Study selection criteria included low back pain of at least 6 months duration with more predominant pain on one side. Patients were excluded if there was a systemic inflammatory disorder, acute pathology on MRI, or involvement in worker’s compensation or litigation among other criteria.

The outcome measures used in this study were a visual analogue scale (VAS) for pain, measured at baseline, 3 weeks and 8 weeks, and a 50% reduction was considered a response. The Oswestry Low Back Pain Questionnaire (OLBPQ) was used to measure functional ability at baseline and at 8 weeks. This measure has 10 different subscales (pain, personal care, lifting, walking, sitting, standing, sleeping, sex, social life, and traveling) each rated 0 to 5. Responders were required to show a 2-point reduction on the pain sub-score and at least one of other subscales. Three patients withdrew or were lost to follow-up over the course of the 8-week study, and these subjects were included in the intent-to-treat analysis as non-responders. Patients were injected with 40 units of Botox (Allergan, Inc) at five lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on one side of the back only, depending on predominance of pain.
At baseline, pain scores on the VAS in the treated group ranged from 6 to 10, with an average of 7.5; in the placebo group, scores ranged from 5 to 10, with an average of 7. At 3 weeks, 73.3% of treated patients and 25% of placebo showed a response on VAS scores (p=0.012). This difference in VAS scores remained significant at 8 weeks with 60% of treated patients and 12.5% of placebo patients still responding (p=0.009). The OLBPQ assessment at 8 weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders (p=0.011).

These results show clinically significant and statistically significant improvements in treated patients as compared with placebo on all three outcome assessments. However, this is only one suggestive study that included 31 subjects, and replication of these findings would be desirable. The population with chronic low back pain is a heterogeneous population, and results in this small group of selected subjects cannot be used to generalize results for the whole population with chronic low back pain. Furthermore, studies should examine the long-term effectiveness of using repeated courses of botulinum toxin to determine the durability of repeated treatments.

2005-2006 Update
A Medline search of the literature from January 2005 to December 2006 was done and did not identify any randomized clinical trials that would lead to a change in the policy statement.

2007 Update

Refractory Urinary Incontinence
Two small randomized controlled trials and a number of published case series have examined the use of botulinum toxin in the management of urinary incontinence, both neurogenic and idiopathic. Ghei et al. conducted a randomized, placebo-controlled crossover study of 20 patients 18 to 80 years old with detrusor overactivity unresponsive to oral antimuscarinic agents. They were injected with either placebo (20 ml normal saline) or botulinum toxin B (5,000 IU) intravesically in the outpatient department of a London hospital. After 6 weeks the treatments were crossed over without washout. The primary endpoint was the paired difference in average void volumes. Secondary endpoints were urinary frequency, number of incontinence episodes and paired differences in quality of life measured by the King's Health Questionnaire. The investigators observed clinically and statistically significant paired differences in the primary endpoint, as well as in urinary frequency and incontinence episodes. Patients had a median of 19 (range 12-42) weekly incontinence episodes at baseline, which was reduced to 1.5 (0-2.8) on active treatment (p=0.001 by Wilcoxon signed-rank test). The same subjects experienced a median 12 episodes a week during the placebo period.

The second RCT was conducted by Schurch et al. 40 The authors treated 59 patients with urinary incontinence caused by neurogenic detrusor overactivity due to spinal cord injury or multiple sclerosis with single dose intramuscular detrusor injections of botulinum toxin A 200 or 300 units or placebo, using a randomized parallel group design. Changes in daily frequency of urinary incontinence episodes over 24 weeks were monitored by patient diaries. Key urodynamic assessments provided objective measures of bladder function. Quality of life was assessed using the Incontinence Quality of Life Questionnaire. Results: Active treatment groups experienced significant decreases in incontinence episodes from baseline (p < 0.05). Active treatment patients also had significant improvements in bladder function and quality of life. Benefits were observed from week 2-24. No safety concerns were raised.

Published case series included both adult and pediatric patients. Results of the better studies are presented in the following table:

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<tr>
<th>Ref</th>
<th>Subjects</th>
<th>Type</th>
<th>Dose/Route</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>41</td>
<td>26</td>
<td>Pediatric</td>
<td>Neurogenic</td>
<td>10U/Kg, inadverturor</td>
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<tr>
<td>42</td>
<td>75 adults</td>
<td>Idiopathic</td>
<td>100, 150 or 200U inadverturor</td>
<td>35-40% had “excellent” result @ 3 months Higher dose was not more effective, but longer duration &amp; more side effects</td>
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<tr>
<td>43</td>
<td>21</td>
<td>Pediatric</td>
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2008 Update

Five small studies of botulinum toxin Type A or Type B intramuscular injections in piriformis syndrome patients were found. These were of variable quality, but consistently positive results (3-4 units mean decrease in 10 point VAS pain scale scores).

Response was noted within the first month, and persisted to the end of the studies (10-16 weeks). Therefore, 2-3 months post injection seems to be a reasonable time to assess the effect of a trial.

2009 Update

There are several head-to-head clinical trials comparing the efficacy and safety of botulinum toxins in patients with cervical dystonia (spasmodic torticollis), blepharospasm, hemifacial spasms, and hyperhidrosis available in the literature. Most of these studies have been conducted in patients with cervical dystonia. While the overall quality of these studies is less than optimal, they all consistently show available botulinum toxins provide an improvement in symptoms from baseline, rather than cure, and suggest all are equally efficacious and durable for the management of these indications at studied dosages.

Numerous randomized, blinded placebo-controlled trials are available for all approved products for on and various off-label indications. However, indirect comparison of this evidence is difficult due to unknown dose bioequivalency, differences in study designs, methodologies, and populations/indications studies, etc.

The Pharmacy and Therapeutics Committee recommended the addition of Dysport to the policy at the November 24, 2009 meeting.

2010 Update

This policy update includes key evidence for FDA-approval of incobotulinumtoxinA (Xeomin), approval of onabotulinumtoxin A (Botox) for treatment of adults with chronic migraine, and strengthens policy language related to recent FDA warnings and actions regarding use and potential therapeutic interchange of these products.

**IncobotulinumtoxinA (Xeomin)**

IncobotulinumtoxinA (Xeomin) is a serotype A botulinum toxin manufactured without accessory proteins that is FDA-approved to improve head position and neck pain in adults with cervical dystonia and for the treatment of blepharospasm in adults previously treated with onabotulinumtoxinA (Botox).

Key evidence for the efficacy and safety of Xeomin in cervical dystonia comes from one phase III, randomized, double-blind, placebo-controlled study (N=233) and one phase III, randomized, double-blind, active-controlled, non-inferiority study (N=463). In the first study, two doses of Xeomin (120 units and 240 units) were compared with placebo. A significant improvement from baseline to Week 4 in mean total Toronto Western Spasmodic Torticollis Scale (TWSTRS) score was observed in both Xeomin dose groups vs. placebo (each p<0.001). Adverse events were reported in 56.4% of Xeomin 120U-treated patients, 55.6% of Xeomin 240U-treated patients, and 41.9% of the placebo group. The most commonly reported adverse events in Xeomin-treated patients were dysphagia, neck pain, and weakness, and each occurred more frequently in the 240U dose group.

In the second study, dosing was approximately 140U for both treatments. Non-inferiority of incobotulinumtoxinA (Xeomin) vs. onabotulinumtoxinA (Botox) was demonstrated by similar significant improvements from baseline to Week 4 in mean total TWSTRS score (-6.6 for Xeomin and -6.4 for Botox, each p<0.0001). There were also no significant differences between the treatments in secondary efficacy endpoints. Incidence of adverse events was 28.1% in the Xeomin group and 24.1% in the Botox group. Dysphagia was the most commonly observed adverse event with either treatment.

Key evidence for the efficacy and safety of Xeomin in blepharospasm consists of one phase III, multicenter, randomized, double-blind, placebo-controlled study in 109 patients with blepharospasm and a stable therapeutic response to Botox and one randomized, double-blind, active-controlled, non-inferiority study (N=300). In the first study, patients randomly received up to 50 units of Xeomin or placebo per eye and then were followed for up to 20 weeks. The primary efficacy endpoint, change from baseline to week 6 in Jankovic Rating Scale (JRS)
severity subscore (assessed by blinded independent investigator) significantly improved in the Xeomin group compared with the placebo group (p<0.001), and the difference (-1.0) was clinically relevant. Median time to onset of effect was 4 days and duration of effect was 10.6 weeks. There were also no significant differences between the treatments in secondary efficacy endpoints. Adverse events were reported by 70.3% of the Xeomin group and 61.8% of the placebo group. The most common adverse events reported in patients treated with Xeomin were eyelid ptosis, dry eye, and dry mouth.

In the second study, patients randomly received up to 35 units of Xeomin or Botox per eye and were followed for up to 16 weeks. Dosing of Xeomin was equivalent to the patient’s dose of Botox prior to study entry. Non-inferiority of Xeomin compared with Botox was demonstrated by similar significant improvements from baseline to Day 21 in mean change in JRS sum score (-2.90 for Xeomin and -2.67 for Botox, each p<0.0001 vs. baseline). No significant differences between the treatments in secondary efficacy endpoints were found. Median onset of effect (4 days) and median duration of effect (110 days) were similar between the treatments. The adverse event profile was similar between the treatments and the most common adverse event overall was ptosis.

While it has been purported that incobotulinumtoxinA might be less immunogenic due to its lack of accessory proteins, this has not been conclusively demonstrated.

**OnabotulinumtoxinA (Botox) for Chronic Migraine**

The efficacy and safety of Botox for the treatment of chronic migraine were evaluated in two similarly designed multi-national, 56-week studies that included a 24-week, 2 injection, double-blind phase comparing Botox to placebo followed by a 32-week, 3 injection, open-label phase (Phase II Research Evaluating Migraine Prophylaxis Therapy [PREEMPT] 1 and 2). In PREEMPT 1 (n=679), the primary outcome, change from baseline in frequency of headache episodes during the double-blind treatment phase, did not differ significantly between the treatment groups. Headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group (p=0.344). The number of migraine episodes also did not differ significantly. There was a decrease of 4.8 migraine episodes in the Botox group and 4.9 in the placebo group, p=0.206. In contrast, there was a significantly greater decrease in the number of headache days and the number of migraine days in the Botox group compared to the placebo group. The protocol of the PREEMPT 2 trial (n=705) was amended to make frequency of headache days the primary endpoint of this study. In PREEMPT 2, change from baseline in frequency of headache days during the double-blind treatment phase differed significantly between groups and favored Botox treatment. The number of headache days decreased by a mean of 9.0 in the Botox group and 6.7 in the placebo group, a difference of 2.3 days per 28 days (p<0.001). The number of migraine days also decreased significantly, more in the Botox group compared to the placebo group, a mean of 8.7 versus 6.3, p<0.001. In contrast to PREEMPT 1, there was a significantly greater decrease in headache episodes in the Botox group than the placebo group, 5.3 versus 4.6, p=0.003. Change in frequency of migraine episodes was not reported.

A pooled analysis from these studies (Dodick et al., 2010) included a total of 1,384 chronic migraine patients who had either never received or were not using any concurrent headache prophylaxis during a 28-day baseline, had at least 15 headache days per month, at least 50% of which were migraine/probable migraine, and had at least 4 distinct headache episodes per month. All patients were randomized to receive placebo or 155 – 195 Units of Botox every 12 weeks for the 2-injection, double-blind treatment phase, and up to 3 additional injections (once every 12 weeks) during the open-label phase. The primary efficacy endpoint for the pooled analysis was mean change from baseline in frequency of headache days for the double-blind treatment phase. Key secondary variables included frequency of migraine days, frequency of moderate/severe headache days, number of cumulative hours of headache on headache days, and frequency of headache episodes. At week 24, Botox treatment provided greater improvements from baseline compared to placebo in frequency of headache days (p<0.001), frequency of migraine days (p<0.001), number of moderate/severe headache days (p<0.001), total cumulative hours of headache on headache days (p<0.001), and frequency of headache episodes (p=0.009). Adverse reactions reported by ≥2% of Botox-treated patients and more frequently than in placebo-treated patients in double-blind, placebo-controlled clinical trials in chronic migraine included headache, facial paresis, eyelid ptosis, bronchitis, neck pain, musculoskeletal stiffness, muscular weakness, myalgia, musculoskeletal pain, muscle spasms, injection site pain, and hypertension.

There are several issues worth noting regarding the methodology and findings of the PREEMPT studies. There was a statistically significant difference in headache episodes in PREEMPT 2 but not PREEMPT 1 (for which it was the primary outcome); the primary outcome for PREEMPT 2 was changed after initiation of PREEMPT 1. Moreover, one of the main secondary outcomes in PREEMPT 1, change in the number of migraine episodes, was not reported in the second trial; the authors did not discuss this omission. In addition, the individual studies did not
include a threshold response to treatment, e.g., at least a 50% reduction in headache or migraine frequency, as a key outcome. The pooled analysis of the 2 trials did report response rates, but these were presented as secondary efficacy outcomes. Other issues, pointed out in opinion pieces included: (1) the majority of patients in both trials fulfilled criteria for medication overuse headache and therefore may have been experiencing secondary headaches rather than chronic migraines, and (2) the clinical relevance of the study findings, i.e., less than a 2-day difference in reduction of headache days per month, is uncertain.

**Other**
Although similar in certain aspects, Botox, Dysport, Xeomin, and Myobloc are unique products that are not interchangeable. They are chemically, pharmacologically, and potentially clinically distinct. The units of biological activity of one botulinum toxin product cannot be compared to nor converted into units of any other botulinum toxin product.

**2012 Update**
A Cochrane Database systematic review of botulinum toxin for subacute/chronic neck pain failed to find a difference from placebo injections that was either statistically or clinically significant. The authors included randomized and quasi-randomized trials. Nine studies with a total of 503 subjects met the selection criteria. Low quality evidence also did not indicate a difference between botulinum toxin injections versus a combination of placebo injections, physical therapy and analgesics. No improvement in disability or quality of life was seen up to six months follow up. A review of botulinum toxin in secondary headaches and cranial neuralgias also failed to provide evidentiary support for this treatment. A cohort of 68 patients diagnosed with medication overuse headache was randomized to receive onabotulinum toxin A or placebo injections. The active treatment group did not experience a significant reduction in headache frequency, but their medication use was reduced. A Cochrane Database review of botulinum toxin in treating lower back pain did not find sufficient evidence to reach a conclusion regarding its effectiveness. In conclusion, no new evidence was found that would require modification of the existing medical necessity criteria for the botulinum toxin products.

**2013 Update**
The FDA has now approved Botox (onabotulinum toxin A) for treatment of overactive bladder (OAB) symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), urinating often (frequency) in adults 18 years and older when another type of medicine (anticholinergic) does not work well enough or cannot be taken and to treat leakage of urine (incontinence) in adults 18 years and older with OAB due to neurologic disease who still have leakage or cannot tolerate the side effects after trying an anticholinergic medication.

Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in 1,105 patients with symptoms of OAB not caused by a neurological condition who were suffering with urinary incontinence for at least 6 months experienced at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days, and who were inadequately treated with an anticholinergic therapy. Patients were randomly assigned to treatment with 100 units of onabotulinum toxin A or placebo injections into the detrusor (bladder) muscle, followed by a re-treatment injection with onabotulinum toxin A after a minimum of 12 weeks in qualified patients, if desired. (To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days.) In both studies, there was a statistically significant decrease in the number of daily urinary incontinence episodes in patients treated with onabotulinum toxin A versus placebo (P<0.001) at week 12.1. In study 1 the onabotulinum toxin A group saw a mean reduction of 2.5 episodes from a baseline of 5.5 versus the placebo group with a mean reduction of 0.9 episodes from a baseline of 5.1 episodes. In study 2 the onabotulinum toxin A group saw a mean reduction of 3.0 episodes from a baseline of 5.5 versus the placebo group with a mean reduction of 1.1 episodes from a baseline of 5.7 episodes.

**Sialorrhea**
Numerous randomized placebo-controlled trials have evaluated the use of botulinum toxins in the treatment of sialorrhea caused by various neurologic disorders, including cerebral palsy, ALS and Parkinson’s disease. These studies have employed both botulinum toxins (A and B), with a variety of specific products and injection techniques in both pediatric and adult patients. Vashishta et al. recently published the results of a meta-analysis of 8 placebo-controlled RCTs involving a total of 181 patients, in which botulinum toxin injected into major salivary
glands produced significant reductions in quantitative measures of drooling severity, standardized mean difference -1.54 (95% CI -2.05 to -1.04). Doses of greater than 50 U produced much stronger effects. The authors concluded that, although efficacy has been demonstrated, further work is needed to identify the optimum dose and injection protocol.

2014 Update
A literature search was conducted from January 2013 to June 4, 2014. A 2013 review discusses 3 randomized controlled trials of intramuscular botulinum toxin for lower back pain. The first of these studies (N=31), by Foster et al. (already referenced in Chronic Low Back section) found that the number of individuals experiencing a > 50% reduction in VAS pain scores when compared with baseline was significantly higher in the botulinum toxin A group (200U) compared with placebo at both 3 weeks (73% vs 25%, p = 0.012) and 8 weeks (60% vs 13%, p = 0.009) post-injection. In addition to this, a 2010 study (N=27) assessed pain relief of subjects with mechanical lower back pain due to bilateral myofascial pain syndrome involving the iliopsoas and/or the quadratus lumborum muscles. Subjects randomly received botulinum toxin A injection (50 units) in one affected side and control injection (0.9% NaCl or 0.25% bupivacaine) in the contralateral side. This study found no significant reductions in visual analog scale (VAS) scores, or improvements in daily life activities or psychological status in comparison with contralateral control treatments. This evidence further supports the current recommendation (investigational) regarding the use of botulinum toxin for the treatment of chronic lower back pain.

Three randomized-controlled trials comparing botulinum toxin to placebo in trigeminal neuralgia (TN) showed significant improvements in VAS pain scores and reduction in attack frequency (1 study) compared with placebo. The first of these studies assessing pain reduction in intractable TN (N=20), found a significant reduction in VAS scores at 12 weeks when comparing injected botulinum toxin A (40-60 units) vs placebo injection (P < 0.0001). A second study (N=36) also found that injected onabotulinum toxin A (50 units) produced a significant reduction in VAS scores at 3 months post-treatment compared with placebo (P = 0.01). A final trial (N=42) assessed the primary endpoints of pain severity and pain attack frequency when comparing treatment with botulinum toxin A (75U) with placebo. Treatment with botulinum toxin significantly reduced pain intensity at 2 weeks (P<0.05) and pain attack frequency at week 1 (P<0.05) post-treatment, with these effects persisting through the remainder of the 12 week trial. Treatment of TN with botulinum toxin was generally well-tolerated, with adverse effects including facial asymmetry and transient edema in the injection area, with dissipation within 7 days of treatment.

2015 Update
A literature search was conducted from January 1, 2014 to June 28, 2015. No studies were found that would indicate need for policy changes. Literature references updated.

References

39. The Company Pharmacy and Therapeutics Committee reviewed and approved on September 25, 2007.
41. Schurch B, De Séze M, Denys P et al. Botulinum toxin type A is a safe and effective treatment for


43. Kuo HC. Will suburothelial injection of small dose of botulinum A toxin have similar therapeutic effects and less adverse events for refractory detrusor overactivity? *Urology* 2006;68:993–998.


69. Reviewed by Premera Pharmacy and Therapeutics Committee in November 2010; January 2012.

**Coding**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>64612</td>
<td>Chemodenervation of muscle(s); muscles(s) innervated by facial nerve (e.g., for blepharospasm or hemifacial spasm)</td>
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<tr>
<td></td>
<td>64615</td>
<td>Chemodenervation of muscle(s); innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine)</td>
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<tr>
<td></td>
<td>64616</td>
<td>Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis)</td>
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<tr>
<td></td>
<td>64617</td>
<td>Chemodenervation of muscle(s); larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography,</td>
</tr>
</tbody>
</table>
Chemodenervation of extraocular muscle when performed

Electrical stimulation for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)

Needle electromyography for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)

- **HCPCS**
  - J0585 Injection, onabotulinumtoxinA, 1 unit (Botox)
  - J0586 Injection, abobotulinumtoxinA, 5 units (Dysport)
  - J0587 Injection, rimabotulinumtoxinB, 100 units (Myobloc)
  - J0588 Injection, incobotulinumtoxinA, 1 unit

- **Type of Service**: Prescription
- **Drug**: Inpatient/Physician's Office

### Appendix

N/A

### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
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<tbody>
<tr>
<td>03/03/98</td>
<td>Add to Prescription Drug Section - New Policy</td>
</tr>
<tr>
<td>08/17/99</td>
<td>Replace Policy - Policy updated; cross-references added.</td>
</tr>
<tr>
<td>12/21/00</td>
<td>Replace Policy - Policy updated, policy statement suggests that botulinum toxin treatment of anal fissure may be considered medically necessary, treatment for headache is considered investigational. New 2001 CPT code added.</td>
</tr>
<tr>
<td>06/19/01</td>
<td>Replace Policy - Policy revised to include discussion of MyoBloc and further discussion of headaches; policy statement revised to include cervical dystonia.</td>
</tr>
<tr>
<td>05/13/03</td>
<td>Replace Policy - Policy updated; policy statement suggests that Botulinum toxin treatment of anal fissure may be considered medically necessary. Policy replaces BC.5.01.05 by allowing treatment for headaches after following specific criteria.</td>
</tr>
<tr>
<td>05/11/04</td>
<td>Replace Policy - Policy was revised to include tension headaches as medically necessary and excluding cervicogenic and cluster headaches as investigational. Rationale section updates and references added.</td>
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<tr>
<td>09/01/04</td>
<td>Replace Policy - Policy renumbered from PR.5.01.112. No changes to dates.</td>
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<tr>
<td>05/10/05</td>
<td>Replace Policy - Policy reviewed &amp; approved by P&amp;T 3/22/05; policy statement is unchanged.</td>
</tr>
<tr>
<td>02/14/06</td>
<td>Replace Policy - Policy reviewed and approved by P&amp;T 1/31/06; codes updated; policy statement is unchanged.</td>
</tr>
<tr>
<td>06/16/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
</tr>
<tr>
<td>06/15/07</td>
<td>Cross Reference Update - No other changes.</td>
</tr>
<tr>
<td>11/13/07</td>
<td>Replace Policy - Policy updated with literature review. Policy statement to include “The use of botulinum toxin may be considered medically necessary as a treatment of urinary incontinence caused by neurogenic or idiopathic overactive detrusor in patients who are refractory to anticholinergic agents”. Reviewed by P&amp;T committee on September 25, 2007. References added.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>Replace Policy - Policy updated with literature search. Piriformis syndrome added as medically necessary. Rationale and References updated. Reviewed by P&amp;T committee on March 25, 2008.</td>
</tr>
</tbody>
</table>

02/08/11  Replace Policy - Policy updated with literature review. Medically necessary FDA-labeled indications for upper limb spasticity and prophylaxis of headaches in adults added with dosage criteria; clarification to off-label medically necessary indications for spastic conditions has been added. A notation has been added to the Policy section indicating all botox drugs have been listed in one lump and that provider’s are responsible to prescribe based upon FDA- or compendium-approval. References have been added and codes have been updated. Policy reviewed by P&T November 2010.

04/08/11  Codes Updated - Code Q2040 added to policy; replaces C9278.

01/25/12  Codes updated: HCPCS code J0588 added to policy to replace Q2040, deleted 12/31/11.

02/14/12  Replace policy. Policy updated with literature search References added. Reviewed by P&T January 24, 2012.

10/17/12  Update Related Policies – Add 7.01.135.

11/7/12  New CPT codes added, 52287 and 64615 effective 11/2/12. HCPCS code Q2040 was removed; it was deleted as of 12/31/11.

02/11/13  Replace Policy. Policy updated with new FDA indications for the treatment of overactive bladder symptoms, such as urge urinary incontinence, urgency and frequency in patients 18 years and older when another anticholinergic has failed or cannot be tolerated; and, for patients 18 years and older with overactive bladder symptoms (incontinence) due to neurologic disease who cannot tolerate the side effects of anticholinergic medication once tried. ICD-9 codes 788.31 and 788.33 added to the policy. Related policies on urinary incontinence added (1.01.17, 2.01.27 and 2.01.60).

06/10/13  Replace policy. Policy updated with the additional of sialorrhea as an additional medically necessary indication; Rationale section updated. References 71 -74 added.

10/16/13  Update Related Policies. Change title to policy 7.01.135.

12/23/13  Coding Update. CPT codes 64613 and 64614 discontinued effective 12/31/13.

07/31/14  Annual Review. Policy updated with literature review; references 72 – 76 added. Trigeminal neuralgia (cranial nerve V) added to the list of medically necessary indications. Coding update: CPT codes 64616 and 64617 added to policy replacing 64613 64614, respectively which were deleted effective 12/31/13; 31513, 31570-71; 43201, 43626 and 52287 removed ICD-9 diagnosis codes also removed – they are not utilized in adjudication of the policy.

09/16/14  Update Related Policies. Remove 2.01.527 as it was archived.

10/22/14  Update Related Policies. Remove 7.01.135 as it was archived.

07/14/15  Annual review. Policy updated with literature review; no change in policy statements. References added.

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