Botulinum Toxins (BOTOX, DYSPORT, MYOBLOC and XEOMIN)

Policy Number: MM.04.004
Original Effective Date: 03/14/2006
Line(s) of Business: HMO; PPO
Current Effective Date: 10/01/2011
Section: Prescription Drugs
Place(s) of Service: Office

I. Description

Botulinum is a family of toxins produced by the anaerobic organism Clostridia botulinum. There are seven distinct serotypes designated as type A, B, C-1, D, E, F, and G. In the United States, four preparations of botulinum are commercially available, three using type A serotype and one using type B. The three formulations of botulinum toxin type A are onabotulinumtoxinA (BOTOX), abobotulinumtoxinA (DYSPORT), and incobotulinumtoxinA (XEOMIN). RimabotulinumtoxinB contains botulinum toxin type B (MYOBLOC). When administered intramuscularly, all botulinum toxins reduce muscle tone by interfering with the release of acetylcholine from nerve endings.

Although similar in certain aspects, each botulinum toxin product is chemically, pharmacologically, and clinically distinct, and is not interchangeable with any other botulinum toxin product. The U.S. Food and Drug Administration (FDA) labeling states that units of biological activity [of one botulinum toxin product] cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

The FDA-approved label for BOTOX (onabotulinumtoxinA) states that it is indicated:

- Treatment of upper limb spasticity in adult patients to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis),
- Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia,
- Treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents,
- Treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above,
On October 15, 2010, the FDA approved Botox injection for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting four hours a day or longer).

The FDA-approved label for DYSPORT (abobotulinumtoxinA) states that it is indicated for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naive and previously treated patients.

The FDA-approved label for XEOMIN (incobotulinumtoxinA) states that it is indicated for:

- Treatment of adults with cervical dystonia to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naive and previously treated patients,
- Treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA (BOTOX).

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

II. Criteria/Guidelines

Botulinum toxin is covered (subject to Limitations/Exclusions and Administrative Guidelines) for the following indications:

A. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury)
B. Strabismus
C. Blepharospasm or facial nerve (VII) disorders (including hemifacial spasm)
D. Upper limb spasticity
E. Prevention of chronic migraine headache
   1. Initial six-month trial (i.e., two series of injections) in adult patients who:
      a. will be receiving treatment by a neurologist or pain management specialist who will be using the FDA-approved prescribing dosage protocol;
      b. have a current diagnosis of migraine with headaches on ≥ 15 days per month for at least 3 months; and
      c. have symptoms that persist despite a meaningful therapeutic trial of at least one agent from two different classes of medications used in the prophylaxis of chronic migraine headaches, i.e., antidepressants, antihypertensives and anticonvulsants, or all of these agents are contraindicated.
   2. Continuation of therapy beyond six months is covered if the patient is significantly benefiting from the therapy.
F. Dystonia/spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with any of the following:
   1. Focal dystonias:
      a. Focal upper limb dystonia (e.g., organic writer’s cramp)
b. Oromandibular dystonia (orofacial dyskinesia, Meige syndrome)
c. Laryngeal dystonia (abductor spasmodic dysphonia)
d. Idiopathic (primary or genetic) torsion dystonia
e. Symptomatic (acquired) torsion dystonia

2. Spastic conditions:
   a. Cerebral palsy
   b. Spasticity related to stroke
   c. Acquired spinal cord or brain injury
   d. Hereditary spastic paraparesis
   e. Spastic hemiplegia
   f. Neuromyelitis optica
   g. Multiple sclerosis or Schilder’s disease

G. Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates

H. Sialorrhea (drooling) associated with Parkinson disease

I. Chronic anal fissure

J. Incontinence due to detrusor overreactivity (urge incontinence), either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis), that is inadequately controlled with anticholinergics.

K. Secondary gustatory hyperhidrosis

L. Severe primary hyperhidrosis in the small subset of patients listed below:
   1. Patients who are inadequately managed with topical agents and
   2. Patients with sweating that is intolerable and that interferes with the patient's daily activities with a Hyperhidrosis Disease Severity Scale score of a 3 or 4
      a. Score 3: "sweating is barely tolerable and frequently interferes with my daily activities."
      b. Score 4: "sweating is intolerable and always interferes with my daily activities."

III. Limitations/Exclusions

A. The use of botulinum toxin is not covered for other indications as payment determination criteria are not met. This includes, but is not limited to:
   1. headaches except as noted above for the prevention of chronic migraine headache,
   2. chronic low back pain,
   3. joint pain,
   4. mechanical neck disorders,
   5. neuropathic pain after neck dissection,
   6. myofascial pain syndrome,
   7. pain after hemorrhoidectomy or lumpectomy,
   8. tremors such as benign essential tremor (upper extremity),
   9. tinnitus,
   10. sialorrhea (drooling) except that associated with Parkinson disease,
   11. chronic motor tic disorder, and tics associated with Tourette's syndrome (motor tics),
   12. lateral epicondylitis,
   13. benign prostatic hyperplasia,
   14. interstitial cystitis,
15. and detrusor sphincteric dyssynergia (after spinal cord injury).
B. Botulinum toxin is not covered for cosmetic indications such as for the treatment of wrinkles.
C. The use of assays to detect antibodies to botulinum toxin is not covered as payment determination criteria are not met.

IV. Administrative Guidelines
A. Precertification is required for the initial six months of therapy for the prevention of migraines. To precertify, please complete HMSA's Drug Review Request and mail or fax the form as indicated. The following documentation from the medical record must be submitted:
1. Neurologist or pain specialist attestation that they will be using the FDA-approved prescribing dosage protocol,
2. Clinical notes supporting a diagnosis of migraine, number of headaches per month, and previous trial and failure of other medications used for prophylaxis of migraine headaches.
B. Precertification is required for continuation of therapy for the prevention of migraines. Documentation from the medical record indicating the patient's response to treatment must be submitted.
C. Other covered indications as noted in this policy do not require precertification. See covered diagnoses listed below. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.
D. Injection of the vocal cords is done in association with laryngoscopic guidance. As indicated by CPT codes 31513, 31570, or 31571, laryngoscopy is considered an integral part of the procedure and separate billing for laryngoscopy and injection is not warranted.
E. Botulinum toxin as a treatment of achalasia requires a separate endoscopy procedure, which is billed separately. CPT established two codes (43201 and 43236) for upper GI endoscopy procedures with submucosal injection, any substance. These codes could apply to the use of botulinum toxin for the treatment of achalasia.

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<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>31513</td>
<td>Laryngoscopy, indirect; with vocal cord injection</td>
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<tr>
<td>31570</td>
<td>Laryngoscopy, direct, with injection into vocal cord(s), therapeutic</td>
</tr>
<tr>
<td>31571</td>
<td>with operating microscope or telescope</td>
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<tr>
<td>43201</td>
<td>Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing, with directed submucosal injection(s) any substance</td>
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<td>43236</td>
<td>Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic, with or without collection of specimen(s) by brushing or washing, with directed submucosal injection(s), any substance</td>
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<td>HCPCS Code</td>
<td>Description</td>
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<tr>
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<td>J0586</td>
<td>Injection, abobotulinumtoxinA, 5 units (this code is for DYSPORT)</td>
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<td>J0587</td>
<td>Injection, rimabotulinumtoxinB, 100 units (this code is for MYOBLOC)</td>
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<td>Injection, incobotulinumtoxin a, 1 unit (this code is for XEOMIN)</td>
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<tr>
<th>ICD-9-CM Code</th>
<th>Description</th>
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<tr>
<td>333.6</td>
<td>Genetic torsion dystonia</td>
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<td>Athetoid cerebral palsy</td>
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<td>Spasmodic torticollis excludes: tortocollis NOS (723.5) hysterical (300.11) pschogenic (306.0)</td>
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<td>333.84</td>
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<td>Other facial nerve disorders (includes facial myokymia, Melkersson’s syndrome)</td>
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<td>Achalasia and cardiospasm</td>
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<td>788.30 - 788.39</td>
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ICD-10 codes are provided for your information. These will not become effective until 10/1/2013:

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<th>ICD-10-CM Code</th>
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<td>Dystonia, unspecified</td>
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<td>Other specified trigeminal nerve disorders</td>
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<td>G51.4</td>
<td>Facial myokymia</td>
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<td>G81.10 - G81.14</td>
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<td>Convergence excess</td>
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V. Scientific Background

This section discusses the evidence for off-label uses of botulinum toxin. The literature review focuses primarily on randomized placebo-controlled clinical trials.

Urologic Applications

*Detrusor overactivity*

Two small blinded, randomized, published in 2005 and 2007 respectively, randomly assigned patients with detrusor overactivity (urge incontinence) due to neurogenic origin that was inadequately controlled with anticholinergic therapy to receive either botulinum toxin or placebo injection into the detrusor muscle. (28, 29) One study reported that botulinum toxin A was used but did not state the specific agent. (28) The other study was a randomized placebo-controlled double-blinded trial with 31 patients that specifically evaluated Dysport for treating neurogenic detrusor overactivity. (29) The two studies reported significant improvements in urodynamic measures, voiding function, and quality of life favoring botulinum toxin treatment. Benefits of botulinum toxin treatment are supported by several open-label trials, summarized in a 2003 review by Sinha and colleagues. (30) In 2008, Karsenty et al. conducted a systematic review of studies of Botox intradetrusor injections in adults with neurogenic detrusor overactivity refractory to anticholinergics and concluded that botulinum toxin treatment results in a clinically significant improvement. (31)

Two small blinded, RCTs randomly assigned patients with idiopathic detrusor overactivity refractory to anticholinergics to botulinum toxin or placebo injected intravesically. For each trial, authors reported significant improvements in maximum capacity, frequency, urgency, and quality of life with botulinum
toxin treatment. (32, 33) One trial used botulinum toxin B (Myobloc) and the other used a botulinum toxin A agent.

**Detrusor sphincter dyssynergia**

In 2002, deSeze and colleagues studied 13 patients with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord disease (traumatic injury, multiple sclerosis, congenital malformations), randomly assigned to receive perineal botulinum toxin A or lidocaine injections into the external urethral sphincter. (34) In the botulinum group, there was a significant decrease in the primary outcome of post-void residual volume compared to no change in the control group receiving a lidocaine injection. Improvements were also seen in the satisfaction scores and other urodynamic outcomes.

In 2006, Karsenty and colleagues (35) reviewed trials of botulinum toxin injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor-sphincter dyssynergia and nonneurogenic obstructive sphincter dysfunction. In the former group, the authors cite 10 small studies (N ranged from 3 to 53; 3 studies included patients in both categories). Most patients were quadriplegic men unable to perform self-catheterization or patients (of both genders) with multiple sclerosis. All except 2 studies were case reports or case series. The previously cited study by deSeze et al. (34) was included; the other RCT enrolled only 5 patients. While most studies report significant improvements, in this study, small patient numbers, different causes of dysfunction, and different outcome measures, together with lack of control arms make it difficult to draw conclusions regarding this application.

**Benign prostatic hyperplasia**

The rationale for botulinum treatment is based on the theory that symptoms of BPH are in part due to a static component related to prostate size and a dynamic component related to the contraction of smooth muscle within the gland. Botulinum therapy addresses this latter component. In 2003, Maria and colleagues reported on 30 patients with BPH, randomly assigned to receive either intraprostatic botulinum toxin A or saline injection. (36). Inclusion criteria for this trial included moderate-to-severe symptoms of BPH based on the American Urological Association (AUA) score and a mean peak urinary flow rate of no more than 15 mL per second with a voided volume of 150 mL or less. After 2 months, the AUA symptom score decreased by 65% among those receiving botulinum toxin, compared to no significant change in the control group. The mean peak urinary flow rate was significantly increased in the treatment group.

In 2006, Chuang and Chancellor (37) reviewed trials testing the use of botulinum toxin in benign prostatic hyperplasia. With the exception of the previously cited trial by Maria and colleagues (36), all were small, open-label trials (n ranged from 8 to 52) that generally reported improvement in spontaneous voiding and decreases in post-void residual volume compared to baseline. No additional RCTs were found in a MEDLINE search through June 2008. Given the prevalence of BPH, larger trials that compare the role of BPH with other medical and surgical therapies are warranted.
**Interstitial cystitis**

Several case series (n ranged from 10 to 19) of botulinum toxin treatment of patients with interstitial cystitis for alleviation of chronic pain and improving bladder capacity have been published. (38-43) All report subjective improvement in a majority of patients, and statistically significant improvement in various measured parameters such as pain by visual analog scale, frequency, nocturia, and functional bladder capacity. The results suggest efficacy but need confirmation in a larger population and preferably in controlled clinical trials.

**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, however most reports are case reports or case series. One RCT, published in 1995, studied 10 patients with essential head tremor. (44) Patients were randomly assigned to receive either botulinum toxin or placebo injections into the sternocleidomastoid and splenius capitus muscle. Five patients improved in the treatment group compared to three in the control group but the difference was not significant. Two randomized, placebo-controlled studies addressed essential hand tremors, the 2001 trial enrolled 133 patients, and the 1996 trial enrolled 25 patients. (45, 46) In both studies, inconsistent significant advantages for botulinum toxin were found on tremor symptom scales, but none were shown on functional outcomes. Thus, the clinical significance of these findings is unclear, and botulinum toxin is considered investigational for treating tremors, such as benign essential tremor.

**Sialorrhea (Drooling)**

Five small (n ranged from 16 to 48) RCTs evaluated botulinum toxin injection into parotid/submandibular glands compared with placebo injection to control sialorrhea in patients with neurological diseases (e.g. Parkinson’s, cerebral palsy, ALS). Ondo and colleagues (47) randomly assigned 16 patients with Parkinson disease to receive placebo or 2,500 U of botulinum toxin B (Myobloc). The botulinum toxin group had significantly better outcome than the placebo group at 1 month on 4 drooling outcomes but groups did not differ on salivary gland imaging and a dysphagia scale. Mancini and colleagues (48) assigned 20 patients to injections of either a saline placebo or 450 U of Dysport. The treatment group was significantly better than placebo on a drooling scale at 1 week, the effect disappeared by 3 months. Lipp and colleagues (49) randomly assigned 32 patients to either placebo or 3 different doses of Dysport: 37.5 U, 75 U, or 150 U. One outcome was an objective measure of drooling based on weight of dental rolls, which significantly favored botulinum toxin over placebo for only the 75 U dose. The same pattern was observed for a patient-measured count of sialorrhea-related acts. Loss to follow-up was 21% at 3 months and 44% at 6 months; it was unclear what follow-up period was represented in the statistical analyses.

In 2006, Lagalla et al. randomly assigned 32 patients with Parkinson’s disease to placebo or 50 U botulinum toxin A; evaluation at 1 month post-injection resulted in significant improvements,
compared with placebo, in drooling frequency, saliva output, and in familial and social embarrassment. (50) Dysphagia scores were not significantly improved. Reid et al. randomly assigned 48 children with cerebral palsy and other neurological disorders to no treatment or to 25 U botulinum toxin A. (51) Maximal response on the Drooling Impact Scale questionnaire occurred at 1 month but the difference between treatment arms remain statistically significant at 6 months. Sixteen of 24 treated were responders. A systematic review of botulinum toxin for treatment of sialorrhea concluded that the ideal dose, injection location, and technique of injection administration remain to be determined. (52) While some questions remain, studies on those with Parkinson disease provide consistent findings related to impact on sialorrhea. Thus, for this specific disease indication, this use of botulinum toxin is considered medically necessary. For sialorrhea associated with other disorders, there is little evidence and additional studies are needed; these indications are considered investigational.

**Chronic Low Back Pain**

Only 1 randomized controlled study of botulinum toxin A treatment in patients with low back pain has been published. (53) The trial, published in 2001, enrolled 31 consecutive patients with chronic low back pain of at least 6 months' duration and more predominant pain on one side. Patients were injected with 40 units of Botox (Allergan, Inc.) at 5 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 8 weeks, 60% of treated patients and 12.5% of placebo patients showed improvement in VAS pain scores (p=0.009). Perceived functional status (Oswestry scale) at 8 weeks showed that 66.7% of treated patients and 18.8% of placebo patients were responders (p=0.011). 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. Botox is considered investigational for low back pain.

**Headache**

The interest in using botulinum toxin as a treatment of headache stemmed from the observation that patients receiving pericranial injections of botulinum toxin for other reasons reported a decrease in the incidence in migraine. While it may exert its effect by relieving the muscle tension associated with migraine, others have proposed independent actions, none yet proven, that may directly affect pain. Research has also addressed other types of headache. Because of the typically high placebo response rate in patients with headache, assessment of evidence focuses on randomized, placebo-controlled trials.

Botulinum toxin for treatment of pain from migraine and from chronic tension-type headaches, was addressed in a TEC Assessment that was completed in 2002 and updated in 2004. (2) Both TEC Assessments concluded that the evidence was insufficient for either indication. More recent studies have focused on the use of botulinum toxin to reduce the frequency of headaches. The American Academy of Neurology (AAN) assessment from 2008 identified three trials on botulinum toxin for episodic migraine, four studies on chronic daily headache, and four studies on chronic tension-type
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headaches. (54) Most of the studies identified by the assessment stated that botulinum toxin A was used, and several further specified that they used Botox. The assessment concluded that botulinum toxin should not be considered for episodic migraine and chronic tension-type headache, and that the evidence was insufficient for treatment of chronic daily headache.

**Migraine Headache**

Migraines can be categorized, among other characteristics, according to headache frequency. According to the Second Edition of the International Headache Classification (ICHD-2), migraine without aura (previously known as common migraine) is defined as at least 5 attacks per month meeting other diagnostic criteria. (55) Chronic migraine is defined as attacks on at least 15 days per month for more than 3 months, in the absence of medication overuse.

A systematic review and meta-analysis of trials on botulinum toxin for treating episodic migraines (fewer than 15 per month over 3 months) was published in 2009 by Shuhendler and colleagues. (56) The investigators identified 8 randomized double-blind placebo-controlled trials evaluating the efficacy of pericranial botulinum toxin A injections. Six additional randomized trials were identified, but they did not meet eligibility criteria because they were not double-blind (n=2), used a measurement scale that was different from other studies (n=1), was not randomized (n=1), included patients with chronic migraine (n=1), or was a subgroup study (n=1). The 8 eligible studies included a total of 1,601 patients. Overall, the mean frequency of migraines per month was 5.3. A pooled analysis of the main study findings found no significant differences between the botulinum toxin A and placebo groups in change in the number of migraines per month. After 30 days of follow-up, the standardized mean difference (SMD) was -0.06 (95% confidence interval [CI]: -0.14 to 0.03, p=0.18). After 90 days, the SMD was -0.05 (95% CI:-0.13 to 0.04, p=0.28). A subgroup analysis that separately examined trials using low-dose botulinum toxin A (less than 100 units) separately from trials using high-dose botulinum toxin A (100 units or more) did not find a statistically significant effect of botulinum toxin A compared to placebo in either strata.

A pair of multicenter RCTs that evaluated onabotulinumtoxinA (Botox) for chronic migraine was published in 2010. The trials reported findings from the double-blind portions of the industry-sponsored PREEMPT (Phase II Research Evaluating Migraine Prophylaxis Therapy) studies 1 and 2. (57,58) Study designs were similar. Both studies included a 24-week double-blind placebo-controlled phase prior to an open-label phase. (Findings from the open-label phases of the studies have not yet been published). The trials recruited patients meeting criteria for migraine and excluded those with complicated migraine. To be eligible for participation, patients needed to report at least 15 headache days during the 28-day baseline period, each headache lasting at least 4 hours. At least 50% of the headaches needed to be definite or probable migraine. The investigators did not require that the frequent attacks occurred for more than 3 months or exclude patients who overused pain medication, 2 of the ICHD-2 criteria for chronic migraine. Eligible patients were randomly assigned to receive 2 cycles of injections of Botox 155 U or placebo, with 12 weeks between cycles. Randomization was stratified based on the frequency of acute headache pain medication during baseline and whether or not they overused acute headache pain medication. (Medication overuse was defined as baseline intake of simple analgesics on at least 15 days or other medications for at least 10 days and medication
use at least 2 days per week). The primary endpoint in PREEMPT 1 was mean change from baseline in frequency of headache episodes for 28 days ending with week 24. A headache episode was defined as a headache with a start and stop time indicating that pain lasted at least 4 hours. Prespecified secondary outcomes included, among others, change in frequency of headache days (calendar days in which pain lasted at least 4 hours), migraine days (calendar days in which a migraine lasted at least 4 hours), and migraine episodes (migraine with a start and stop time indicating that pain lasted at least 4 hours). Based on availability of data from PREEMPT 1 and other factors, the protocol of the PREEMPT 2 trial was amended (after study initiation but before unmasking) to make frequency of headache days the primary endpoint of this study. The authors noted that, to control for potential Type-1 error related to changes to the outcome measures, a more conservative p value, 0.01 instead of 0.05, was used. Several quality of life measures were also included in the trials. This includes the 6-item Headache Impact Test (HIT-6) and the Migraine Specific Quality of Life Questionnaire (MSQ v.2). Key findings of the 2 studies are described below.

PREEMPT 1 randomly assigned a total of 679 patients. (57) The mean number of migraine days during baseline was 19.1 in each group. The mean number of headache episodes during the 28-day baseline period was 12.3 in the Botox group and 13.4 in the placebo group. Approximately 60% of patients had previously used at least 1 prophylactic medication and approximately 68% overused headache pain medication during baseline. A total of 296/341 (87%) in the Botox group and 295/338 (87%) in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline in frequency of headache episodes over a 28-day period, did not differ significantly between groups. The number of headache episodes decreased by a mean of 5.2 in the Botox group and 5.3 in the placebo group (p=0.344). Similarly, the number of migraine episodes 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 decrease in frequency of headache days was 7.8 in the Botox group and 6.4 in the placebo group, a difference of 1.4 headache days per 28 days, p=0.006. Corresponding numbers for migraine days were 7.6 and 6.1, respectively, p=0.002. There was significantly greater improvement in quality of life in the Botox versus the placebo group. The proportion of patients with severe impact of headaches (i.e., HIT-6 score at least 60) in the Botox group decreased from 94% at baseline to 69% at 24 weeks and in the placebo group decreased from 95% at baseline to 80%. There was a between-group difference of 11%, p=0.001. The authors did not report scores on the Migraine Specific Quality (MSQ) of Life Questionnaire but stated that there was statistically significant greater improvement in the 3 MSQ role function domains at week 24, restrictive (p<0.01), preventive (p=0.05), and emotional (p<0.002). Adverse events were experienced by 203 patients (60%) in the Botox group and 156 patients (47%) in the placebo group. Eighteen patients (5%) in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. Treatment-related adverse events were consistent with the known safety profile of Botox.

PREEMPT 2 randomly assigned a total of 705 patients. (58) The mean number of migraine days during baseline period was 19.2 in the Botox group and 18.7 in the placebo group. The mean number of headache episodes during the 28-day baseline period was 12.0 in the Botox group and 12.7 in the placebo group. Approximately 65% of patients had previously used at least 1 prophylactic medication, and approximately 63% overused headache pain medication during baseline. A total of 311/347 (90%
in the Botox group and 334/358 (93%) in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline in frequency of headache days over a 28-day period (a different primary outcome than PREEMPT 1) 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 compared to the placebo groups, 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.

Similar to PREEMPT 1, quality of life measures significantly improved in the Botox versus the placebo group. The proportion of patients with severe impact of headaches in the Botox group decreased from 93% at baseline to 66% at 24 weeks and in the placebo group decreased from 91% at baseline to 77%. There was a between-group difference of 10%, p=0.003. The authors reported statistically significantly greater improvement in the three MSQ role function domains at week 24, restrictive, preventive and emotional (p<0.001 for each domain). Adverse events were experienced by 226 patients (65%) in the Botox group and 202 patients (56%) in the placebo group. Fifteen patients (4%) in the Botox group and 8 (2%) in the placebo group experienced serious adverse events. As in PREEMPT 1, treatment-related adverse events were consistent with the known safety profile of Botox.

Also published in 2010 was a pooled analysis of findings from the PREEMPT 1 and PREEMPT 2 studies; this analysis was also industry-sponsored. (59) There were 688 patients in the Botox group and 696 in the placebo group in the pooled analysis of outcomes at week 24. In the combined analyses, there was a significantly greater reduction in change from baseline in frequency of headache days, migraine days, headache episodes and migraine episodes in the Botox compared to placebo groups. For example, the pooled change in frequency of headache days was a mean of 8.4 in the Botox group and 6.6 in the placebo group, p<0.001. The mean difference in number of headache days over a 28-day data collection period was 1.8 (95% CI=1.13 to 2.52). The pooled change in frequency of headache episodes was 5.2 in the Botox group and 4.9 in the placebo group, a relative difference of 0.3 episodes (95% CI=0.17 to 1.17, p=0.009). Between-group differences, though statistically significant, were relatively small and may not be clinically significant. In the pooled analysis, the authors also reported the proportion of patients with at least a 50% decrease from baseline in the frequency of headache days at each time point (every 4 weeks from week 4 to week 24). For example, at week 24, the proportion of participants with at least a 50% reduction in headache days was 47.1% in the Botox group and 35.1% in the placebo group. In contrast, the difference in the proportion of patients experiencing at least a 50% reduction in headache episodes did not differ significantly between groups at 24 weeks or at most other time points, with the exception of week 8. The article did not report the proportion of participants who experienced at least a 50% reduction in migraine days or migraine episodes. The pooled analysis had statistically significant findings for the change in proportion of patients with severe headache impact according to the HIT-6 and change in MSQ questionnaire domains.

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 was changed after initiation of PREEMPT
1. Moreover, 1 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 individuals studies did not include threshold response to treatment, e.g., at least a 50% reduction in headache or migraine frequency, as a key outcome. The pooled analysis did report response rates, but these were presented as secondary efficacy outcomes.

An editorial that discusses the findings of the PREEMPT studies commented that the majority of patients in both trials fulfilled criteria for medication overuse headache, and therefore many patients may have been experiencing secondary headaches rather than chronic migraines. (60) If patients did have secondary headaches, detoxification alone may have been a sufficient treatment to change their headache pattern to an episodic one. Another opinion piece, published after the PREEMPT 1 and 2 studies, mentioned that the clinical relevance of less than a 2-day difference in reduction in number of headache days is uncertain. (61) The author of the second article noted, though, that this degree of reduction in headache days is similar to that previously found in several medication trials.

The published evidence does not suggest that botulinum toxin improves net health outcome for patients with an episodic pattern of migraines (i.e., fewer than 15 episodes per month); thus it is considered investigational. There were 2 published studies (PREEMPT 1 and 2) on Botox for chronic migraine (at least 15 episodes per month); these were conducted by the same research group, were industry-sponsored, and had nearly identical designs. The PREEMPT 1 and 2 had a number of statistically significant findings, but the clinical significance of these results was unclear. The proportion of patients who responded to treatment was reported in the pooled analysis, but not in the individual trials. Based on data from the PREEMPT trials, FDA approval and clinical input obtained in 2010, botulinum toxin is considered medically necessary for the prevention of chronic migraine in certain situations, i.e., patients were diagnosed with chronic migraine who failed trials of other medications.

**Tension Headache**

Nine RCTs of botulinum toxin for treatment of chronic tension-type headaches have been published. The studies included in the AAN assessment (62-65) are described in table E-4 of the AAN supplemental information (accessible online at http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). The type of agent was not specified for the headache trials. Other RCTs in the treatment of tension headache include Smuts et al. 1999, (66), Rollnick et al. 2000, (67), Rollnick et al. 2002, (68), Rollnik et al. 2001, (69), Schmitt et al. 2001, (70) and Straube et al. 2008. (71). Two were rated AAN Class I, 3 Class II, and 4 Class IV. Five trials enrolled fewer than 20 patients per treatment arm. One very small Class III trial reported statistically significant differences favoring treatment in change in mean tenderness and in headache severity (56); no primary outcome identified; another small Class III trial reported a significantly higher percentage of patients with a greater than 50% decrease in headache score. (66) All other trials reported no significant difference between trial arms for the primary outcome. Thus, the higher quality evidence for this indication shows no significant effect for botulinum toxin treatment of chronic tension-type headache, and botulinum toxin is considered investigational.

**Chronic Daily Headache**
Although this category is not recognized in the International Classification of Headache Disorders, it is commonly defined to include different kinds of chronic headache such as chronic or transformed migraine and daily persistent headache, and may also include chronic tension-type headache, addressed separately here. The studies included in the AAN assessment (72-75) are described in Table E-4 of the AAN supplemental information (available online at http://www.neurology.org/content/vol70/issue19/images/data/1707/DC1/Tables_e-1_to_4.doc). An additional RCT in the treatment of chronic daily headache published since the AAN assessment is Freitag et al. 2008 (76). All were rated AAN Class II, enrolled at least 20 patients per treatment arm, and administered botulinum toxin-A, including doses in the range of 100–200 U. Two studies reported significant improvement in primary outcomes, while the other 3 reported no significant differences. The evidence is conflicting and insufficient for conclusions; thus this remains an investigational indication.

Cluster Headache

No controlled trials have been reported on this type of headache.

Cervicogenic Headache

Three RCTs, published between 2000 and 2008, randomly assigned patients with chronic headache related to whiplash injury to botulinum toxin A treatment or placebo. (77-79) One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant. (79) Another reported no significant differences in any of several pain-related outcomes. (78) One trial reported a significant improvement in pain with treatment while the placebo group reported no improvement, but the study design was flawed in that the placebo group reported less pain at baseline. (77) The evidence from these trials is conflicting and insufficient for conclusions. A Cochrane Review of treatment of mechanical neck disorders, published in 2007, (80), included 6 RCTs (total N=273) of botulinum toxin compared to placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of 4 studies (total N=139) for pain outcomes gave a nonsignificant result. The authors concluded that a range of doses have not shown significant differences compared to placebo or to each other. Thus, botulinum toxin is considered investigational for this indication.

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. Seven randomized, blinded, placebo-controlled clinical trials of botulinum toxin versus placebo for cervicothoracic myofascial pain syndrome have been reported. All trials injected botulinum toxin or placebo into trigger points in the upper back, shoulder, and/or cervical muscles. Total botulinum toxin doses varied considerably across trials as did numbers of
patients enrolled (n=20 to 132) and methods of pain assessment. Five trials reported no significant differences in response between treatment and placebo. (81-85) The majority of trials specified that botulinum toxin A was used. One trial, administering high-dose botulinum toxin versus placebo, reported significant differences in pain relief at marginal p values. (86) The last trial reported significant differences in only a few of several outcome measures. (87)

Two RCTs compared botulinum toxin to dry needling and to lidocaine or bupivacaine injection. In one trial published in 2005, lidocaine trigger point injection was significantly more effective than dry needling but significantly less effective than botulinum toxin. (88) In the other, both bupivacaine and botulinum toxin A were similarly effective and not significantly different. (89)

Three studies addressed another form of myofascial pain, piriformis syndrome, characterized by buttock tenderness and sciatica. One study of nine patients compared botulinum toxin with placebo, finding that postinjection pain scores were significantly improved in the treatment group for only one of four pain domains, while none improved in the placebo group. (90) Another study of 36 patients had a high loss to follow-up (23 percent) and found that the botulinum toxin group had a significantly higher proportion with 50 percent or greater reduction in pain on each of the last two follow-up visits, compared with placebo. (91) These small and flawed studies, both published in 2002, do not establish that the effects of botulinum toxin exceed those of placebo. A third study from 2000, comparing botulinum toxin with methylprednisolone, found better results for the former, but placebo effects were not considered. (92) The evidence for piriformis myofascial pain syndrome does not support conclusions about the effects of botulinum toxin.

One RCT enrolled patients with myofascial pain related to bruxism; while subjective and objective improvements in several outcomes measures were reported favoring treatment versus placebo; none was significant. (93)

A 2007 systematic review (94) selected RCTs of trigger-point injection; use of the Oxford Pain Validity Scale was also a selection criterion. Five trials were included; one trial resulted in a significant effect, whereas the other four did not. The data were described as "limited and clinically heterogeneous" and the authors concluded that the evidence did not support the use of botulinum toxin A injections in trigger points for myofascial pain. Due to the lack of consistent evidence of benefit, botulinum toxin is considered investigational for treatment of myofascial pain syndrome.

Wound Healing and Pain Control

Three small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published (95 Davies et al. 2003, n=50; 96 Patti et al. 2005, n=30; 97 Patti et al. 2006, n=30). Davies and colleagues (95) showed marginal improvement in pain control at days 6 and 7 by patient VAS scores (p<0.05) with Botox injections; there was no significant difference in morphine or analgesic use. Patti et al. (96) randomly assigned patients to 20 U botulinum toxin or saline injection and reported significantly decreased duration of postoperative pain at rest and during defecation in the treated group. Patti and colleagues (97) found significant differences in postoperative maximum resting pressure change from baseline comparing botulinum toxin treatment to topical
glyceryl nitrate (p<0.001; resting pressure is increased after surgery and may be responsible for pain). In addition, there was a significant reduction in postoperative pain at rest (p=0.01) but not during defecation. There was no difference in time of healing. These small studies suggest improvement in pain control, however, differences may be small and need confirmation in larger trials.

In 2006, Gassner and colleagues (98) conducted a small, RCT of botulinum toxin-induced immobilization of facial lacerations to improve wound healing compared to placebo (n=31). The outcome was determined by blinded assessment of photographs of wound healing at intervals using a VAS. The authors report enhanced wound healing in the treatment arm (8.9 vs. 7.2, p=0.003). These results conflict with the wound-healing outcome after hemorrhoidectomy, as reported by Patti and colleagues that same year. (97) Additional studies are necessary to identify indications and confirm improved outcomes; thus, botulinum toxin is considered investigational for wound healing.

Pelvic and Genital Pain in Women

One small, open-label trial from 2006 (99) tested botulinum toxin A injections into painful vulvar tissue to alleviate provoked vestibulodynia (n=19). Patients receiving either of 2 doses had significantly reduced pain compared to baseline for 8 (lower dose) to 14 weeks (higher dose). A prospective cohort study tested different doses of botulinum toxin in 12 women with pelvic floor muscle hypertonicity and history of chronic pelvic pain. (100) Compared to baseline, there were nonsignificant reductions in pelvic pain and nonsignificant improvements in quality of life. In a double-blinded, randomized, placebo-controlled trial, (101) botulinum toxin was injected into pelvic floor muscles to attempt to alleviate chronic pelvic pain (n=60). Pain scores were reduced for both groups, but there were no significant differences between groups. The placebo response was underestimated, and the trial likely underpowered for the outcome. The evidence is insufficient for this indication.

Neuropathic Pain after Neck Dissection

Two open-label trials of 16 and 23 patients who had failed conservative therapy investigated various doses of botulinum toxin A injected into the area of complaint. (102, 103) For both studies, which were conducted by the same group, results indicated significant reductions in pain compared to baseline and trends toward improved quality of life. However, lack of a randomized, placebo-controlled study design to control for strong placebo effects in pain therapy render these studies inconclusive.

Chronic Pain after Lumpectomy

There are no relevant publications on the use of botulinum toxin for pain following mastectomy or lumpectomy.

Lateral Epicondylitis and Other Joint Pain

In 2005, Wong and colleagues reported on the results of a double-blind, placebo-controlled trial that randomly assigned 60 patients with lateral epicondylitis of at least three months’ duration to receive either a single intramuscular injection of botulinum toxin or placebo, targeted at the tender spot in the
elbow. (104) In the botulinum group, the mean visual analogue score improved from 65.5 mm to 25.3 mm at four weeks, compared to a change of 66.2 mm to 50.5 mm in the placebo group, a statistically significant difference. Mild paresis was reported in four patients in the botulinum group. In a similarly designed study of 40 patients, published in 2005, Hayton and colleagues reported no treatment effect at three months. (105) However, the injection site was targeted at five cm distal to the most tender spot, and a different formulation of botulinum toxin was used. In a randomized, blinded, placebo-controlled trial of 130 patients, a single injection of botulinum toxin into the painful origin of the forearm extensor muscles was tested versus placebo. (106) Treated patients were significantly improved overall at weeks 2, 6, 12, and 18. Continuous pain was significantly improved in the treated group only at weeks 6 and 18; maximum pain showed no improvement compared to placebo.

Two case series of patients with chronic joint pain refractory to conservative management studied the effect of botulinum toxin A injections (one series specified that Dysport was used) into several joints of patients with arthritis and into the knee joint of patients with chronic knee pain. (107, 108) Both reported significant improvement in joint pain and function compared to baseline, lasting for 3-12 months. Although the results of several trials of botulinum toxin injections into joints for chronic pain tend to favor treatment, some results are contradictory. Due to the lack of consistent findings from well-designed studies, botulinum toxin for treatment of lateral epicondylitis and other joint pain is considered investigational.

Tinnitus

In 2005, Stidham and colleagues explored the use of botulinum toxin A injections for tinnitus treatment under the theory that blocking the autonomic pathways could reduce the perception of tinnitus. (109) In this study, 30 patients were randomly assigned in a double-blind study to receive either 3 subcutaneous injections of botulinum toxin A around the ear followed by placebo injections 4 months later, or placebo injections first followed by botulinum toxin A. The authors reported that 7 patients had reduced tinnitus after the botulinum toxin A injections, which was statistically significant when compared to the placebo groups in which only 2 patients reported reduced tinnitus (p<0.005). The tinnitus handicap inventory scores were also significantly decreased between pretreatment and 4 months post-botulinum toxin A injections. However, no other significant differences were noted when comparing the two treatments at 1 and 4 months after injections. The authors noted larger studies are needed. Also, study limitations, including size and lack of intent-to-treat analysis limit interpretation of results. Due to insufficient evidence from large randomized trials, botulinum toxin for tinnitus is considered investigational.

Antibody Testing for Botulinum Toxin Resistance

Rare patients have no response to initial administration of botulinum toxin (primary resistance) and a small percentage of adult patients develop secondary resistance after long-term treatment. Reasons for resistance include injection of incorrect muscles, unrealistic expectations of a complete cure, and interference from associated disorders that interfere with perception of response. (110) In approximately 3%-10% of adult patients, true secondary resistance arises due to the development of antibodies that specifically neutralize the activity of botulinum toxin. (111-114) That neutralizing
antibodies directly cause resistance has been shown in a case study in which a patient with severe dystonia, secondary resistance, and detectable neutralizing antibodies was treated with repeated plasma exchange and depletion of serum antibodies; subsequent treatment with the same botulinum toxin type was successful. (115) Non-neutralizing antibodies may also develop in patients but have no effect on outcomes. The predisposing factors are not completely understood but include use of higher doses, shorter intervals between repeat treatments, and younger age. (112,116) In 2 studies of pediatric patients treated for spasticity, neutralizing antibodies were detected in 28%–32% of patients. (117, 118) Recommendations for avoiding eventual resistance are to use the lowest dose possible to obtain a clinical response, and schedule intervals of 10–12 weeks between injections, if possible. (110)

Patients who develop secondary resistance to botulinum toxin A may stop treatment for several months and then undergo retreatment with likely success; however, the duration of response is often short, as neutralizing antibodies may re-develop quickly. (112,119) Alternatively, the patient may be administered botulinum toxin B, with which neutralizing antibodies to toxin A will not interfere. However, the duration of effect is shorter, and adverse effects have occurred at higher frequencies than for botulinum toxin A. (116, 120)

Confirmation of neutralizing antibodies to botulinum toxin A in research studies has most often been accomplished with either protection of mice from lethal doses of toxin with injection of patient serum (121) or with an in vitro toxin-neutralizing assay based on a mouse diaphragm nerve-muscle preparation. (122) While sensitive, neither assay is appropriate for a clinical laboratory setting. Other assay formats have been explored, such as immunoprecipitation, Western blot, and enzyme-linked immunosorbent assay (ELISA). However, unless only the protein sequences that specifically react with neutralizing antibodies are employed, these formats detect both neutralizing and non-neutralizing antibodies (117, 123-124) and would therefore result in significant numbers of false-positive results. Thus, the currently available testing approach is considered investigational. An option for some patients might be to inject toxin into the frontal muscle above one eyebrow; a toxin-responsive patient would have asymmetry of the forehead on attempted frowning, whereas, a nonresponsive patient would not. (123)

Physician Specialty Society and Academic Medical Center Input

In response to requests, clinical input was received on this policy when it was under review in 2008 and again in 2010. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. In 2008, input was received on a number of indications from 5 physician specialty societies and 3 academic medical centers while this policy was under review in 2008. Nearly all reviewers who provided input agreed with the investigational determination for use in headaches and on the investigational role for antibody testing. Among the 4 reviewers who commented on use in sialorrhea, 2 reviewers felt this was medically necessary and 2 disagreed. In 2010, input was received only on botulinum toxin for migraine from 4 physician specialty societies (7 reviews) and 4 academic medical centers. The majority of reviewers agreed with the investigational indication for episodic migraine. Several reviewers thought that
Botulinum toxin was medically necessary in patients with disabling and/or frequent episodic migraines that were refractory to other treatments. Clinical input was more divergent for use of botulinum toxin for chronic migraine; some agreed that use was investigational and others did not. Reviewers who thought that botulinum toxin was medically necessary for patients with chronic migraines generally thought its use should be limited to patients unresponsive to other treatments.

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References


