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Botulinum Toxins

Policy # 00012

Original Effective Date: 01/28/2003

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Treatment of Hyperhidrosis is addressed separately in medical policy 00172.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Botulinum Toxin Type A

Based on review of available data, the Company may consider the use of botulinum toxin Type A products (Botox[®], Dysport[®], or Xeomin[®]) to be **eligible for coverage** for **any** of the following conditions:

- Strabismus[∞]
- Blepharospasm or facial nerve (VII) disorders (including hemifacial spasm) [∞]
- Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck AND a history of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles[∞]
- Upper limb spasticity[∞]
- Axillary hyperhidrosis that is inadequately managed with topical agents[∞]
- Urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., Spinal Cord Injury, Multiple Sclerosis) in patients who have an inadequate response to or are intolerant of an anticholinergic medication[∞]
- Overactive bladder (OAB) in adults unresponsive to or intolerant of an anticholinergic medication*
- Chronic migraine headaches[∞]:
 - o Prophylaxis of chronic migraine headaches in adult patients (≥ 15 days per month with headaches lasting 4 hours a day or longer); **and**
 - o There is documented failure of, contraindication to, or intolerance of at least two different migraine prophylaxis medications (e.g. beta-blockers, calcium channel blockers, tricyclic antidepressants or anticonvulsant medications) from two different therapeutic drug classes. (Note: This specific patient criterion is a company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Dystonia/spasticity resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in patients with **any** of the following:
 - o Focal dystonias:
 - Focal upper limb dystonia (e.g., organic writer's cramp)
 - Oromandibular dystonia (orofacial dyskinesia, Meige syndrome)
 - Laryngeal dystonia (adductor spasmodic dysphonia)
 - Idiopathic (primary or genetic) torsion dystonia

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- Symptomatic (acquired) torsion dystonia
- o Spastic conditions
 - Cerebral palsy
 - Spasticity related to stroke
 - Acquired spinal cord or brain injury
 - Hereditary spastic paraparesis
 - Spastic hemiplegia
 - Neuromyelitis optica
 - Multiple sclerosis or Schilder's disease
- Esophageal achalasia in patients who have not responded to dilation therapy or who are considered poor surgical candidates
- Sialorrhea (drooling) associated with Parkinson disease
- Chronic anal fissure
- Palmar hyperhidrosis that is inadequately managed with topical agents

∞FDA-approved indication for at least one of the agents

Botulinum Toxin Type B

Based on review of available data, the Company may consider the use of botulinum toxin Type B products (Myobloc[®])[‡] to be **eligible for coverage** for **any** of the following conditions:

- Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury). For this use, cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck and a history of recurrent involuntary contraction of one or more of the muscles of the neck, e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles. ∞
- Sialorrhea (drooling) associated with Parkinson disease
- 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 anticholinergic therapy

∞FDA-approved indication

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers, with the exception of cosmetic indications, the use of all botulinum toxin formulations to be **investigational*** for all other indications (not specifically mentioned above for the requested drug), including but not limited to the following:

- Non-migraine headaches (e.g. cluster headaches, tension-type headaches, etc.)
- Chronic low back pain
- Joint pain
- Mechanical neck disorders
- Neuropathic pain after neck dissection

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- Myofascial pain syndrome
- Pain after hemorrhoidectomy or lumpectomy
- Tremors such as benign essential tremor
- Tinnitus
- Sialorrhea (drooling) except that associated with Parkinson disease
- Chronic motor tic disorder (ICD-9 307.22), and tics associated with Tourette's syndrome (motor tics)(ICD-9 307.23)
- Lateral epicondylitis
- Benign prostatic hyperplasia
- Interstitial cystitis
- Detrusor sphincteric dyssynergia (after spinal cord injury)
- Prevention of pain associated with breast reconstruction after mastectomy
- Hirschsprung's disease
- Gastroparesis
- Facial wound healing
- Internal anal sphincter (IAS) achalasia

Based on review of available data, the Company considers the use of assays to detect antibodies to botulinum toxin to be **investigational**.*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of botulinum toxin Type A products (Botox, Xeomin, or Dysport) in the treatment of chronic migraines in the absence of failure, contraindication, or intolerance to at least two different migraine prophylaxis medications from two different therapeutic drug classes to be **not medically necessary**.**

When Services Are Not Covered

The use of all botulinum toxin formulations as treatment of wrinkles or other cosmetic indications is a contract exclusion and is therefore **not covered**.

Background/Overview

Botulinum is a family of toxins produced by the anaerobic organism *Clostridia botulinum*. Four formulations of botulinum toxin have been approved by the FDA. Labeled indications of these agents differ; however, all are FDA-approved for treating cervical dystonia in adults. Botulinum toxin products are also used for a range of off-label indications.

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 serotype. The drug names of the botulinum toxin products were changed in 2009; trade names and product formulations did not change. The three formulations of botulinum toxin type A are currently called onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport) and incobotulinumtoxinA (Xeomin). Xeomin, the newest product marketed in the U.S., consists of the pure neurotoxin without complexing proteins and is the

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only product that is stable at room temperature for up to four years. Myobloc contains botulinum toxin type B; the current name of this drug is rimabotulinumtoxinB.

All four products are approved by the FDA for the treatment of cervical dystonia in adults; this is the only FDA-approved indication for Myobloc. Dystonia is a general term describing a state of abnormal or disordered tonicity of muscle. As an example, esophageal 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.

Cervical dystonia is a movement disorder (nervous system disease) characterized by sustained muscle contractions. This results in involuntary, abnormal, squeezing and twisting muscle contractions in the head and neck region. These muscle contractions result in sustained abnormal positions or posturing. Sideways or lateral rotation of the head and twisting of the neck is the most common finding in cervical dystonia. Muscle hypertrophy occurs in most patients. When using botulinum toxin to treat cervical dystonia, the postural disturbance and pain must be of a severity to interfere with activities of daily living; and the symptoms must have been unresponsive to a trial of standard conservative therapy. In addition, before using botulinum toxin, alternative causes of symptoms such as cervicogenic headaches must have been considered and excluded.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Among the botulinum toxin products, onabotulinumtoxinA (Botox) is FDA-approved for the largest number of indications. Other than the indications mentioned above, this includes axillary hyperhidrosis in adults and in individuals at least 12 years of age, blepharospasm and strabismus. On October 15, 2010, the FDA approved Botox injection for prevention of chronic migraine. Chronic migraine is defined as episodes that otherwise meet criteria for migraine (e.g., at least 4 hours in duration) that occur on at least 15 days per month for more than 3 months, in the absence of medication overuse. OnabotulinumtoxinA is also approved for treatment of urinary incontinence due to neurogenic conditions causing detrusor overactivity in patients unresponsive to or intolerant to anticholinergic medication. Most recently, in 2013, onabotulinumtoxinA received FDA approval for treatment of overactive bladder (OAB) in adults who are unresponsive to or intolerant to anticholinergic medication.

The newest product, Xeomin, is approved for treating blepharospasm.

Two products, Botox (marketed as Botox Cosmetic) and Dysport, are approved for temporarily improving the appearance of glabellar (frown) lines in adults younger than 65 years of age.

The botulinum toxin products have also been used for a wide variety of off-label indications, ranging from achalasia, spasticity after strokes, cerebral palsy, and anal fissures

Botox®[†] (Allergan, Irvine, CA) was approved by the FDA in 1991, Myobloc®[†] (Solstice Neurosciences) in 2000, Dysport®[†] (Medicis Pharmaceutical Corporation, Scottsdale, AZ) in 2009, and Xeomin®[†] (Merz Pharmaceuticals) in 2010.

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Rationale/Source

The most recent literature search was performed for the period July 2008 through July 2013. For studies published before 2000, it is assumed that Botox, the only FDA-approved agent at that time, was used.

Dystonia/Spasticity

This policy section is based on a 1996 TEC Assessment that focused on the use of botulinum toxin for the treatment of focal dystonia or spasticity (which was updated in 2004), the American Academy of Neurology (AAN) 2008 assessments of movement disorders and spasticity, and additional controlled trials identified by literature searches.

At the time of the 1996 TEC Assessment, only onabotulinumtoxinA (Botox) was commercially available.

Based on the evidence, the TEC Assessment concluded that Botox therapy for the following indications met the BCBSA TEC Criteria:

- Children with cerebral palsy in whom dynamic joint deformity secondary to spasticity or athetosis produces pain and/or interferes with function; and
- Ambulatory and nonambulatory patients with chronic limb spasticity, in whom dynamic joint deformity produces pain and/or interferes significantly with supportive care and quality of life (sitting, balance, hygiene, pain control). (Note: evidence for this indication was derived from trials that enrolled patients with chronic spasticity due to stroke, multiple sclerosis, trauma, familial spastic paresis, Friedrich's ataxia, hypoxic brain damage, motor neuron disease, and hemorrhage from aneurysm.)

In addition, the AAN assessments summarized the evidence and concluded that the evidence was AAN level A (established as effective, should be done) for equinus varus deformity in children with cerebral palsy, and level B (probably effective, should be considered) for upper extremity and for adductor spasticity and for pain control in conjunction with adductor-lengthening surgery in children with cerebral palsy. The evidence was rated level B for treatment of adult spasticity in the upper and lower limb for reducing muscle tone and improving passive function, but insufficient evidence to recommend an optimum technique for muscle localization at the time of injection. The evidence was rated level B for upper focal limb dystonia, but insufficient for lower focal limb dystonia; and was rated level B for adductor laryngeal dystonia but insufficient for abductor laryngeal dystonia. The bulk of the literature is based on trials using onabotulinumtoxinA (i.e., Botox).

In 2013, Foley and colleagues identified 16 randomized controlled trials (RCTs) comparing injection of botulinum toxin to placebo injections or a nonpharmacologic treatment of moderate to severe upper-extremity spasticity following stroke. Studies evaluated the impact of treatment on activity limitations. Ten trials with a total of 1,000 patients had data suitable for pooling. In a pooled analysis of effect size, botulinum toxin was associated with a moderate treatment effect compared to comparison interventions (standardized mean difference [SMD]: 0.54, 95% confidence interval [CI]: 0.35-0.71, $p < 0.001$). The largest RCT was published in 2011 by Shaw and colleagues and included 333 patients with poststroke upper limb spasticity to physical therapy plus Dysport ($n=170$) or physical therapy alone ($n=163$). The primary outcome, improved function at 1 month according to the Action Research Arm Test (ARAT), did not differ significantly among groups. Improved function according to ARAT scores also did not differ significantly

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between groups at 3 or 12 months. Change in muscle tone according to median change in the Motor Assessment Scale (MAS) significantly favored the Dysport group over the placebo group at 1 month (mean change= -0.6 and -0.1, respectively, $p<0.001$), but not at 3 and 12 months.

Several European trials have evaluated Xeomin for poststroke upper limb spasticity. Kanovsky and colleagues randomized 148 patients with poststroke upper limb spasticity to treatment with either Xeomin or placebo. After 4 weeks, a significantly higher response rate was found in all treated flexor muscle groups among patients treated with Xeomin compared to placebo. The treatment benefit lasted through the week-12 visit. An open-label extension of this study with 145 participants was published in 2011. Patients received up to 5 additional sets of Xeomin injections, with 12-week intervals between injections. A total of 111 (77%) patients had at least 3 injections and 72 (50%) had 4 injections. Outcomes were assessed 4 weeks after each injection. Compared to baseline, patients consistently showed improved outcomes at each posttreatment visit. None of the patients developed neutralizing antibodies in either the double-blind or extension phases of the study.

A 2007 systematic review identified 70 studies that examined two botulinum toxin agents used to treat cervical dystonia. There were 30 studies on Botox, 24 on Dysport, 11 on Myoblock and 5 combining 2 agents. Xeomin for treating cervical dystonia has been evaluated in a randomized controlled trial that found it to be non-inferior to Botox.

Strabismus

Strabismus is a condition in which the eyes are not in proper alignment with one another. In 2012, a Cochrane review was published by Rowe and colleagues evaluating the literature on botulinum toxin for strabismus. The investigators identified 4 RCTs, all of which were published in the 1990s. Three trials compared botulinum toxin injection to surgery, and 1 compared botulinum toxin injection to a noninvasive treatment control group. Among the trials that used surgery as a comparison intervention, 2 studies found no statistically significant differences in outcomes between the 2 groups, and 1 found a higher rate of a satisfactory outcome in the surgery group. The study comparing botulinum toxin to no intervention did not find a significant difference in outcomes in the 2 groups. Complications after botulinum toxin included transient ptosis and vertical deviation; combined complication rates ranged from 24% to 56% in the studies.

For patients who failed prior surgery, Tejedor and Rodriguez conducted a trial in 1999 that included 55 children with strabismus who remained symptomatic after surgical alignment. Patients were randomly assigned to receive a second operation (28 patients) or botulinum toxin injection ($n=27$). Motor and sensory outcomes did not differ significantly in the 2 groups. At 3 years, for instance, 67.8% of children in the reoperation group and 59.2% of children in the botulinum toxin group were within 8 prism diopters of orthotropias ($p=0.72$). In 1994, Lee and colleagues randomized 47 patients with acute unilateral sixth nerve palsy to botulinum toxin treatment or a no treatment control group. The final recovery rate was 20 of 25 (80%) in the botulinum toxin group and 19 of 22 (80%) in the control group. Since this treatment is a noninvasive alternative to surgery, it may be considered medically necessary.

Blepharospasm

Blepharospasm is a progressive neurological disorder characterized by involuntary contractions of the eyelid muscles; it is classified as a focal dystonia. Randomized controlled trials have evaluated Botox,

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Dysport and Xeomin for the treatment of blepharospasm and found these agents to be effective at improving symptoms. No randomized controlled trials evaluating Myobloc for treating blepharospasm were identified in literature searches.

Esophageal Achalasia

Esophageal achalasia is a primary motor disorder characterized by abnormal lower esophageal sphincter relaxation. Randomized, placebo-controlled trials initially validated the efficacy of botulinum toxin in treating achalasia. In 1999, Vaezi and colleagues reported a trial that randomized 42 patients with achalasia to receive either botulinum toxin or undergo pneumatic dilation. Pneumatic dilation resulted 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. This conclusion is supported by a 2006 Cochrane systematic review and meta-analysis of 178 patients treated with either botulinum toxin or pneumatic dilation.

A randomized controlled trial by Annese and colleagues in Italy with 78 patients found 100U of Botox and 250U of Dysport to have comparable efficacy for treating esophageal achalasia.

Internal Anal Sphincter (IAS) Achalasia

IAS achalasia is a disorder of defecation in which the internal anal sphincter is unable to relax. Symptoms include severe constipation and soiling. A systematic review of studies on treatment of IAS achalasia was published in 2012 by Friedmacher and Puri. The authors did not identify any RCTs of Botox treatment. Two prospective case series and 14 retrospective case series with a total of 395 patients with IAS achalasia were identified. The majority of patients in the series, 229 of 395 (58%), were treated with posterior IAS myectomy and 166 (42%) were treated with intrasphincteric botulinum toxin injection. A meta-analysis of data from the observational studies found that regular bowel movements were more frequent after myectomy (odds ratio [OR]: 0.53, 95% CI: 0.29-0.99, $p=0.44$, $p=0.04$, respectively). Moreover, the rate of transient fecal incontinence was significantly higher after botulinum toxin injection (OR: 0.07, 95% CI: 0.01-0.54, $p<0.01$) and the rate of subsequent surgical intervention was higher after botulinum toxin injection (OR: 0.18, 95% CI: 0.07-0.44, $p<0.001$). Other outcomes, including continued use of laxatives or rectal enemas, and the overall complication rates, did not differ with the 2 treatments. Due to a lack of RCTs, and a meta-analysis of observational data suggesting that posterior IAS myectomy results in greater improvement in health outcomes than botulinum toxin injections, botulinum toxin for treating IAS achalasia is considered investigational.

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 sphincterotomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin is a logical medical approach. In 1998, Maria and colleagues randomized 30 patients with chronic anal fissure to receive either two injections of 20 units of botulinum toxin, on either side of the fissure, or two injections of saline. After two months, 11 patients in the treatment group reported healing, compared to only two in the control group. The four

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patients who still had fissures after two months underwent retreatment with botulinum toxin; two of these four 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 to successfully treat anal fissure. In 1999, Brisinda and colleagues in Italy compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 patients. After two months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group. The same group conducted a second, similar trial in 2007 with 92% versus 70% healing rates for botulinum toxin A-treated versus nitroglycerin ointment-treated patients ($p < 0.001$). Another trial by this research group found that Botox and Dysport used to treat anal fissures were similar in terms of efficacy and tolerability. Others have reported both supportive and contradictory data from randomized trials comparing the same treatments. Randomized, controlled trials of botulinum toxin vs. sphincterotomy have reported significantly better results with sphincterotomy but authors concluded that botulinum toxin was a viable first option for patients who are not good surgical candidates. A systematic review concluded that no single treatment was the best for all patients. A 2012 systematic review of the literature identified 2 RCTs comparing botulinum toxin with placebo, 1 RCT comparing botulinum toxin with lidocaine pomme, 5 RCTs comparing botulinum toxin with nitrates, and 8 RCTs comparing botulinum toxin with surgery. A meta-analysis was not performed due to heterogeneity among studies. The author noted that the studies tended to be small and of short duration, and superiority of botulinum toxin over surgery has not been demonstrated. However, due to the fact that it is a minimally invasive option that can be repeated, it is a reasonable option prior to surgery.

Urologic Applications

Overactive bladder/neurogenic detrusor overactivity. In 2011, Duthie and colleagues published a Cochrane review of RCTs evaluating botulinum toxin injections for treating adults with overactive bladder syndrome. The authors identified 19 trials that compared treatment with botulinum toxin to placebo or another intervention in patients with idiopathic or neurogenic overactive bladder. Two studies included botulinum toxin B; the remainder included botulinum toxin A. The outcomes reported varied, which made it difficult for the authors to pool study findings. A pooled analysis of 3 studies reporting change in urinary frequency episodes at 4-6 weeks reported a significantly better outcome with botulinum toxin injection compared to placebo (pooled mean difference: -6.50; 95% CI: -8.92 to -4.07). A pooled analysis of 3 studies on change in incontinence episodes at 4-6 weeks also found a significantly greater improvement with botulinum toxin (mean difference: -1.58; 95% CI: -2.16 to -1.01). The findings were similar when 2 studies that reported outcomes at 12 weeks were pooled.

Other systematic reviews have included both controlled and uncontrolled studies. A 2013 systematic review by Soljanik identified 28 studies evaluating onabotulinumtoxinA for the treatment of neurogenic detrusor overactivity/neurogenic overactive bladder; 6 of the studies were RCTs. The authors reported that studies with comparative data found superior outcomes with onabotulinumtoxinA compared to placebo. Data from the RCTs were not pooled. Serious adverse events were not reported. However, adverse events after intra-detrusor botulinum toxin injection include postvoid residual urine (50%), urinary retention (23.7%), and urinary tract infection (16.7%). Also in 2013, Mehta and colleagues identified 14 studies evaluating botulinum toxin A for treating neurogenic detrusor overactivity after spinal cord injury; only 1 was an RCT. The authors examined effect sizes interpreted as small, >0.2 ; moderate, >0.5 ; or large, >0.8 . Studies tended to have large effect sizes for outcomes including bladder capacity and reflex detrusor volume. The mean proportion of patients who experienced episodes of incontinence decreased after treatment with botulinum

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toxin A from 23% to 1.3% per day. Previously in 2008, Karsenty et al. identified 18 studies evaluating botulinum toxin A to treat patients who were refractory to anticholinergics. Most of the studies reported statistically significant improvement in clinical and urodynamic outcomes, without major adverse events.

Representative large, double-blind RCTs are described below:

In 2013, Nitti and colleagues published data from an industry-supported study that included 557 patients with overactive bladder and urinary incontinence inadequately controlled by anticholinergics. Patients were randomized to receive an intradetrusor injection of onabotulinumtoxinA 100 U or placebo. At the 12-week follow-up, there was a statistically significantly greater decrease in the daily frequency of urinary incontinence episodes in the group that received botulinum toxin than in the placebo group (-2.65 vs. -0.87, $p < 0.001$). The other primary endpoint was the proportion of patients with a positive response at week 12 according to the treatment benefit scale. A significantly larger proportion of patients in the botulinum toxin group than the placebo group reported a treatment benefit (60.8% vs. 29.2%, $p < 0.001$). A total of 22.9% of patients in the botulinum toxin group and 6.5% of patients in the placebo group became completely continent. In the first 12 weeks after injection, urinary tract infections occurred in 43 of 278 patients (15.5%) in the botulinum toxin group and 16 of 272 patients (5.9%) in the placebo group. Urinary retention was reported by 15 patients (5.4%) in the botulinum toxin group and 1 patient (0.4%) in the placebo group. Between-group p values were not reported for adverse effects.

A 2012 industry-supported RCT by Ginsberg and colleagues included 416 patients with neurogenic detrusor activity associated with multiple sclerosis or spinal cord injury. Patients were randomized to receive injections with 200 U onabotulinumtoxinA, 300 U onabotulinumtoxinA or placebo. Decrease in the mean number of weekly incontinence episodes at week 6, the primary endpoint, was significantly greater in both active treatment groups (-21 in the 200 U group and -23 in the 300 U group) than in the placebo group (-9, $p < 0.001$). Urinary retention was a common adverse event. Among patients who did not catheterize at baseline, 35% in the 200 U group, 42% in the 300 U group and 10% on placebo initiated catheterization. A total of 329 of 416 patients (79%) completed the 52-week study, however, outcomes such as the number of weekly incontinence episodes were not reported at 52 weeks.

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), randomized to receive perineal botulinum toxin A or lidocaine injections into the external urethral sphincter. 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.

Systematic reviews had addressed this potential indication for botulinum toxin injection. Most recently, in 2012, Mehta and colleagues conducted a systematic review of literature on botulinum toxin injection as a treatment of detrusor external sphincter dysfunction and incomplete voiding after spinal cord injury. The authors identified 2 RCTs in addition to uncontrolled studies. The RCTs included the deSeze study, discussed above and a second study that included only 5 patients. A 2008 systematic review by Karsenty and colleagues reviewed trials of botulinum toxin A injected into the urethral sphincter to treat different types of lower urinary tract dysfunction, grouped into neurogenic detrusor-sphincter dyssynergia and non-

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neurogenic 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 2 controlled studies were the same ones included in the Mehta systematic review. Authors of both systematic reviews noted that, while most of the available studies have reported improvements with botulinum toxin injections, there are few published studies, and studies included small numbers of patients. There is insufficient evidence from RCTs on the impact of botulinum toxin on health outcomes for patients with detrusor sphincter dyssynergia; therefore, this indication is considered investigational.

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 2012, Marchal and colleagues published a systematic review of the literature on use of botulinum toxin in treating benign prostatic hyperplasia. The authors identified 25 studies on this topic, including controlled and uncontrolled studies and abstracts published in journal supplements. There were 6 RCTs, 3 published as full articles and 3 as abstracts. Two of the 3 published RCTs were considered to be of sufficient quality for meta-analysis. The authors reported that pre- and posttreatment mean postvoiding residue did not differ significantly; pooled results were not reported for between-group outcomes. One of the RCTs was published by Maria and colleagues in 2003. The investigators reported on 30 patients with BPH randomly assigned to receive either intraprostatic botulinum toxin A or saline injection. 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. Given the prevalence of BPH, larger trials with good methodology that compare the role of botulinum toxin with other medical and surgical therapies for treating BPH are warranted before conclusions can be drawn about the impact of this technology on health outcomes.

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. 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.

There is evidence from multiple RCTs that botulinum toxin is an effective treatment for detrusor overactivity; therefore, this is considered medically necessary. There is insufficient evidence on other urologic applications; thus, for these, botulinum toxin is considered investigational.

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

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investigated in patients with tremors unrelated to dystonias, however most reports are case reports or case series. One randomized controlled trial published in 1995 studied ten patients with essential head tremor. (Patients were randomized 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. 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.

Sialorrhea (Drooling)

Parkinson Disease

Several RCTs have evaluated botulinum toxin injection in patients with Parkinson disease. For example, in 2006, Lagalla et al. randomly assigned 32 patients with Parkinson disease to placebo or 50 U botulinum toxin A; evaluation at 1 month postinjection resulted in significant improvements compared with placebo, in drooling frequency, saliva output, and in familial and social embarrassment. Dysphagia scores were not significantly improved. Moreover, Ondo and colleagues 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. Groups did not differ on salivary gland imaging and a dysphagia scale. Mancini and colleagues assigned 20 patients with Parkinson disease 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.

Cerebral Palsy

In 2012, Rodwell and colleagues published a systematic review of published literature evaluating botulinum toxin injections in the salivary gland for treating sialorrhea in children with cerebral palsy and neurodevelopment disability. The authors identified 5 RCTs; sample sizes in individual trials ranged from 6 to 48 participants. One of the RCTs, which had 6 participants, was terminated due to adverse events. In a pooled analysis from 3 RCTs of data 4 weeks postintervention, the mean score on the Drooling Frequency and Severity Scale (DFSS) was significantly lower in children who received botulinum toxin injections compared to a control intervention (mean difference: -2.71 points, 95% CI: -4.82 to -0.60, $p < 0.001$). The clinical significance of this degree of difference in DFSS scores is not clear. Data were not pooled for other outcomes. The systematic review also identified 11 prospective case series. The rate of adverse events associated with botulinum toxin injection in the RCTs and case series ranged from 2% to 41%. Dysphagia occurred in 2 of the 6 participants in the RCT that was terminated early and in 2 of 126 patients in a case series. There was 1 reported chest infection, 1 case of aspiration pneumonia and, in 1 case series, 6 of 126 patients experienced an increased frequency of pulmonary infections. In 7 studies, there were reports of patients with difficulty swallowing and/or chewing following botulinum toxin treatment.

The largest RCT on botulinum toxin for treating sialorrhea in children with cerebral palsy was published in 2008 by Reid and colleagues. Forty-eight children with cerebral palsy ($n=31$) and other neurologic disorders were randomized to a single injection of 25 U botulinum toxin A compared to no treatment. Drooling was assessed by administering the Drooling Impact Scale. Scores were significantly different between groups at 1 month, and a beneficial effect of botulinum toxin injection remained at 6 months.

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A 2013 article focused on the long-term safety of botulinum toxin A injection for treating sialorrhea in children. The study included 69 children; 47 (68%) had cerebral palsy. Children received their first injection of botulinum toxin at a mean age of 9.9 years and mean follow-up was 3.1 years. During the study period, the children received a total of 120 botulinum toxin injections. Complications occurred in 19 of 69 (28%) children and in 23 of 120 (19%) injections. Fifteen of 23 complications were minor, including 6 cases of dysphagia. There were 8 major complications. These included 3 cases of aspiration pneumonia, 2 cases of severe dysphagia, and 3 cases of loss of motor control of the head. Complications were associated with 5 hospitalizations and 2 cases of neogastric tube placement.

While some questions remain, studies on those with Parkinson disease provide consistent findings related to impact on sialorrhea. Although there is evidence of improvement in drooling scales following botulinum toxin injections in children with cerebral palsy, the clinical significance is uncertain and there are concerns about the safety of injecting botulinum toxin into the salivary gland in this population.

Chronic Low Back Pain

Only one randomized controlled study of botulinum toxin A treatment in patients with low back pain has been published. The trial, published in 2001, enrolled 31 consecutive patients with chronic low back pain of at least six months' duration and more predominant pain on one side. 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 eight 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 eight 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. Botulinum toxin is considered investigational for treatment of chronic 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. Research has also addressed other types of headache.

Chronic 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. Chronic migraine is defined as attacks on at least 15 days per month for more than 3 months, in the absence of medication overuse.

Several RCTs and systematic reviews of RCTs have been published. Most recently, in 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review on preventive pharmacological treatments for migraine in adults. The investigators identified 15 double-blind RCTs evaluating botulinum toxin for migraine prevention; 13 used onabotulinumtoxinA and 2 used



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abobotulinumtoxinA. In a meta-analysis of 3 RCTs, onabotulinumtoxinA was found to be more effective than placebo in reducing the number of chronic migraine episodes per month by at least 50% (risk ratio [RR]: 1.5, 95% CI: 1.2-1.8). In another pooled analysis, onabotulinumtoxinA was associated with a significantly higher rate of treatment discontinuation due to adverse effects than placebo (RR: 3.2, 95% CI: 1.4-7.10). Five RCTs compared the efficacy of onabotulinumtoxinA and another medication (topiramate or divalproex sodium). Findings were not pooled, but for the most part, there were not statistically significant differences in outcomes between the 2 drugs.

In 2012, Jackson and colleagues conducted a meta-analysis of RCTs on botulinum toxin A for the prophylactic treatment of headache in adults; the analysis addressed migraines, as well as other types of headache. The investigators included RCTs that were at least 4 weeks in duration, had reduction in headache frequency or severity as an outcome, and used patient-reported outcomes. The investigators reviewed study eligibility criteria and categorized them as addressing episodic (<15 headaches per month) or chronic headache (at least 15 days per month). A total of 10 trials on episodic migraine and 7 trials on chronic migraine were identified. All of the trials on episodic migraine and 5 of 7 trials on chronic migraine were placebo-controlled; the other 2 trials compared botulinum toxin injections to oral medication. A pooled analysis of the studies on chronic migraine found a statistically significantly greater reduction in the frequency of headaches per month with botulinum toxin versus a control intervention (difference: -2.30, 95% CI: -3.66 to -0.94, 5 trials). In contrast, in a pooled analysis of studies on episodic migraine, there was not a statistically significant difference between groups in the change in monthly headache frequency (difference: -0.05, 95% CI: -0.25 to 0.36, 9 trials).

Previously, in 2009, Shuhendler and colleagues published a systematic review and meta-analysis of trials on botulinum toxin for treating episodic migraines. The investigators identified 8 randomized double-blind placebo-controlled trials evaluating the efficacy of botulinum toxin A injections. 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% 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. Study designs were similar. Both studies included a 24-week double-blind placebo-controlled phase prior to an open-label phase. 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



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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. 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. 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

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334/358 (93%) in the placebo group completed the 24-week double-blind phase. The primary outcome, change from baseline 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 3 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. 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: 1.13-2.52). 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: 0.17-1.17, $p = 0.009$). 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 individual

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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. 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. 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.

Another example of an RCT on botulinum toxin for treating chronic migraine was published by Cady and colleagues. The study included patients who met ICHD-2 criteria for chronic migraine. Patients were randomized to receive treatment with Botox (n=29) or topiramate (n=30). At the 12-week follow-up, the end of the double-blind phase of the study, treatment effectiveness did not differ significantly between groups. For the primary endpoint, Physician Global Assessment at week 12, physicians noted improvement in 19 of 24 (79%) in the Botox group and 17 of 24 (71%) in the topiramate group; 9 patients (15%) were not available for this analysis.

Tension Headache. The 2012 meta-analysis by Jackson and colleagues, discussed above, identified 7 RCTs evaluating botulinum toxin for treating chronic tension-type headaches; all were placebo-controlled. A pooled analysis of these 7 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin versus placebo groups (difference: -1.43, 95% CI: -3.13 to 0.27). The trial with the largest sample size was published by Silberstein and colleagues in 2006. (63) This study included 300 patients randomized to 1 of 4 doses of botulinum toxin or placebo. Overall, there was not a statistically significant difference between the botulinum toxin groups and the placebo group in the mean change from baseline to 90 days in number of headache days per month.

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 2012 meta-analysis by Jackson and colleagues identified 3 RCTs comparing botulinum toxin A to placebo in patients with at least 15 headaches per month. A pooled analysis of data from these 3 trials found a significantly greater reduction in the number of headaches per month in the botulinum toxin versus the placebo group (difference: -2.06, 95% CI: -3.56 to -0.56). Individually, only 1 of the 3 trials, published by Ondo and colleagues in 2004, found a statistically significant benefit with botulinum toxin treatment. This study included 60 patients and included patients with chronic migraines, as well as chronic tension-type headache. The Ondo study found significantly greater reduction in the number of headache-free days over weeks 8 to 12 in the botulinum toxin versus placebo group (p<0.05), but there was not a statistically significant between-group difference in reduction in headache-free days over the entire 12-week study period (p=0.07). The other 2 studies had much larger sample sizes; 355 patients in a study by Mathew and colleagues and 702 patients in a study by Silberstein and colleagues.

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Neither found a statistically significant difference in the reduction in the number of headache days per month with botulinum toxin versus placebo. The available evidence from RCTs is conflicting and insufficient for conclusions; thus chronic daily headache remains an investigational indication.

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

Cervicogenic Headache. In 2011, Linde and colleagues published a double-blind placebo-controlled crossover study that included 28 patients with treatment-resistant cervicogenic headache. Patients were randomized to treatment with botulinum toxin A and placebo, in random order; there was at least an 8-week period between treatments. The trial did not find significant differences between active and placebo treatment in the primary outcome, reduction in number of days with moderate to severe headache. Three other randomized controlled trials, published between 2000 and 2008, randomized patients with chronic headache related to whiplash injury to botulinum toxin A treatment or placebo. One trial reported trends toward improvement with treatment for various outcomes; most were not statistically significant. Another reported no significant differences in any of several pain-related outcomes. 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. The evidence from these trials is conflicting and insufficient for conclusions. A Cochrane Review of treatment of mechanical neck disorders, published in 2007, included six randomized controlled trials (total N=273) of botulinum toxin compared to placebo for chronic neck disorders with or without radicular findings or headache. A meta-analysis of four 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.

Based on the published data, U.S. 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 diagnosed with chronic migraine who failed trials of other medications. For tension headache, RCTs and systematic reviews have been performed. These do not indicate that botulinum toxin improves outcomes. For other headache types, the evidence is scant and insufficient to form conclusions about efficacy.

Myofascial Pain Syndrome

Myofascial pain syndrome is characterized by painful muscles with increased tone and stiffness associated with myofascial trigger points. 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. The optimal study to evaluate the efficacy of botulinum toxin injection for treating myofascial pain syndrome would be double-blind to minimize the placebo effect and would compare injections of botulinum toxin to dry needling and to anesthetic injection. A 2013 systematic review of evidence on botulinum toxin for treating myofascial pain syndrome searched for studies that were double-blind and compared botulinum toxin injection to an alternate intervention. Seven RCTs were identified that met the review's inclusion criteria; all 7 included placebo-control groups. Duration of follow-up in the studies varied from 2 to 6 months. Five of 7 RCTs reported no significant difference between groups in all or nearly all outcomes. In one of the 5, more adverse events were reported by the botulinum toxin group than the saline group. A sixth study reported no significant difference between groups on pain outcomes, but significantly greater improvement in electromyography (EMG) outcomes. The seventh study

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found significantly greater improvement in pain outcomes with botulinum toxin injection compared to placebo. This positive study, by Gobel and colleagues, received the highest score on the methodologic quality instrument used by the review authors. The Gobel study was the only RCT identified to control for cointerventions by not permitting other treatments e.g., nonsteroidal anti-inflammatory drugs, NSAIDs or opioids. The 2013 systematic review did not pool study findings.

A 2011 meta-analysis by Langevin and colleagues of 4 trials comparing botulinum toxin to placebo for chronic myofascial neck pain did not find a statistically significant short-term difference between groups. The pooled standard mean difference (SMD) was -0.21 (95% CI: -0.50 to 0.70). These 4 trials were considered by the authors to have high validity; that is they scored at least 6 on a 12-point risk of bias instrument used by the Cochrane collaboration.

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 1 of 4 pain domains, while none improved in the placebo group. Another study of 36 patients had a high loss to follow-up (23%), and found that the botulinum toxin group had a significantly higher proportion, with 50% or greater reduction in pain on each of the last two follow-up visits, compared with placebo. 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. The evidence for piriformis myofascial pain syndrome does not support conclusions about the effects of botulinum toxin.

Numerous RCTs have been performed for treatment of myofascial pain syndrome. The majority of these trials do not report benefit for botulinum toxin.

Pain Control After Hemorrhoidectomy

Several small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. A 2005 article described a study by Patti and colleagues (n=30) who 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. A 2006 study by Patti and colleagues, which also included 30 patients, 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 healing.

Facial Wound Healing

In 2013, Ziade and colleagues reported on findings of a study including 30 adult patients presenting to the emergency department with facial wounds without tissue loss. Patients were assigned to have an injection of botulinum toxin (n=11) or no injection (n=13) within 72 hours of the suturing of the wounds. The primary outcomes were scores on the following scales at 1 year: Patient Scar Assessment Scale (PSAS), Observer Scar Assessment Scale (OSAS), Vancouver Scar Scale (VSS) and a 1 to 10 visual analogue scale (VAS). The PSAS was a patient-reported outcome, the OSAS and VSS were assessed clinically by a blinded

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independent evaluator and the VAS was assessed using photograph analysis by a team of 6 medical specialists. Patients were not blinded to treatment group, and thus the PSAS might be a more subjective outcome, whereas it is likely that the OSAS, VSS and VAS were all reasonably objectively assessed. Twenty-four of 30 patients (80%) were available for the 1-year follow-up. There were no significant differences between groups in the PSAS, OSAS and VSS scales. For example, the median OSAS score was 8 in the botulinum toxin group and 9 in the control group. However, a significant between-group difference was found on the 4th outcome, the VAS score, favoring the botulinum toxin group. The median VAS score was 8.25 for the botulinum group and 6.35 for the control group, $p < 0.001$. These results demonstrate a lack of consistency in finding a benefit across outcomes, i.e., there was no significant difference in the patient-reported or clinically assessed outcomes, only on the outcome based on photographic analysis. Previously, in 2006, Gassner and colleagues 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 compared to the placebo arm (8.9 vs. 7.2, $p=0.003$). There are few RCTs evaluating botulinum toxin for facial wound healing, and the available trials did not find consistent evidence of benefit.

Pelvic and Genital Pain in Women

One small, open-label trial from 2006 tested botulinum toxin A injections into painful vulvar tissue to alleviate provoked vestibulodynia ($n=19$). Patients receiving either of two doses had significantly reduced pain compared to baseline for eight (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. 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, 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 was 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. 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.

Lateral Epicondylitis and Other Joint Pain

In 2005, Wong and colleagues reported on the results of a double-blind, placebo-controlled trial that randomized 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. 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. However,

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the injection site was targeted at 5 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 A into the painful origin of the forearm extensor muscles was tested versus placebo. 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. 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. In this study, 30 patients were randomized in a double-blind study to receive either three subcutaneous injections of botulinum toxin A around the ear followed by placebo injections four months later, or placebo injections first followed by botulinum toxin A. The authors reported that seven patients had reduced tinnitus after the botulinum toxin A injections, which was statistically significant when compared to the placebo groups in which only two patients reported reduced tinnitus ($p < 0.005$). The tinnitus handicap inventory scores were also significantly decreased between pretreatment and four months post-botulinum toxin A injections. However, no other significant differences were noted when comparing the two treatments at one and four 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. In about 3%–10% of adult patients, true secondary resistance arises due to the development of antibodies that specifically neutralize the activity of botulinum toxin. 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. Nonneutralizing 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. In two studies of pediatric patients treated for spasticity, neutralizing antibodies were detected in 28%–32% of patients. 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.

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Patients who develop secondary resistance to botulinum toxin A may stop treatment for several months and then undergo re-treatment with likely success; however, the duration of response is often short, as neutralizing antibodies may re-develop quickly. 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 side effects have occurred at higher frequencies than for botulinum toxin A.

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 or with an in vitro toxin-neutralizing assay based on a mouse diaphragm nerve-muscle preparation. 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 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.

Chronic Pain after Lumpectomy

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

Pain Associated with Breast Reconstruction after Mastectomy

No randomized controlled trials were identified evaluating botulinum toxin for pain control after mastectomy and expander reconstruction. One published study was identified, an observational study published by Layeeque and colleagues in 2004. The study included 48 patients who were undergoing mastectomy with tissue expander placement. Treatment selection was based on physician preference; 22 (46%) patients had Botox injections to prevent postoperative pain and 26 (54%) patients were treated without Botox. Botulinum toxin was injected into the pectoralis major, serratus anterior, and rectus abdominis insertion. Pain was scored using a VAS of 0 to 10.

Pain-related outcomes tended to be better among patients who received Botox injections. Mean immediate postoperative pain was 3.09 (standard deviation [SD]=0.92) in the botulinum toxin group and 6.80 (SD=1.98) in the standard treatment group, $p<0.0001$. The mean dose of morphine used during the first 24 hours was 3.27 mg (SD=3.18) in the Botox group and 17.15 (SD=10.40) in the standard treatment group, $p<0.0001$. Among the other outcomes, mean length of hospital stay was 26 hours (SD=8) in the Botox group and 37 hours (SD=19) in the standard treatment group; this difference was statistically significant, $p=0.015$. A limitation of the study was that it was not randomized, and there may have been differences between groups that affected outcomes. Findings have not been replicated in large observational studies or RCTs using any of the FDA-approved formulations of botulinum toxin. Thus, botulinum toxin injection to prevent pain associated with breast reconstruction after mastectomy is considered investigational.



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Hirschsprung's Disease

The published literature consists of small case series. The largest prospective case series, published by Minkes and Langer in 2000, included 18 children (median age=4 years) with persistent obstructive symptoms after surgery for Hirschsprung's disease. Patients received injections of botulinum toxin (Botox) into 4 quadrants of the sphincter. The total dose of botulinum toxin during the initial series of injections was 15 U to 60 U. Twelve of 18 (67%) patients experienced improvement for more than 1 month and the remaining 6 (33%) either showed no improvement or improved for less than 1 month. Ten children had 1-5 additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A 2011 series by Patrus and colleagues retrospectively reviewed outcomes in 22 patients with Hirschsprung's disease treated over 10 years who had received a median of 2 (range 1-23) botulinum toxin injections for postsurgical obstructive symptoms. The formulation of botulinum toxin was not specified. Median follow-up (time from first injection to time of chart review) was 5.0 years (range 0 to 10 years). At the time of chart review, 2 of 22 patients (9%) had persistent symptoms. Eighty percent of children had a "good response" to the initial treatment (not defined) and 69% had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after botulinum toxin injection (median=0) compared to preinjection (median=1.5), $p=0.003$. The authors did not report whether or not patients received other treatments during the follow-up period in either case series. A limitation of the case series study design is that it lacks a control group. Due to the lack of controlled studies showing benefit, this indication is considered investigational.

Gastroparesis

A systematic review of the literature, published in 2010, identified a total of 15 studies on botulinum toxin injection to treat gastroparesis. Two of the studies were RCTs; the remainders were case series or open-label observational studies. The authors stated that, while the nonrandomized studies generally found improvement in subjective symptoms and gastric emptying after botulinum toxin injections, the RCTs did not confirm the efficacy of botulinum toxin for treating gastroparesis. The authors concluded that there is insufficient evidence to recommend botulinum toxin for gastroparesis. Brief descriptions of the 2 RCTs are as follows:

In 2007, Arts and colleagues published a randomized cross-over study with 23 patients. The study included consecutive patients at a single institution who had symptoms suggestive of gastroparesis and established delayed gastric emptying for solids and liquids. Patients received, in random order, injections of Botox or saline during gastrointestinal endoscopies, with a 4-week interval between injections. Symptoms were assessed using the Gastroparesis Cardinal Symptom Index (GCSI), which has a maximum score of 45. When data from both groups were combined, there were no statistically significant differences in improvement after botulinum toxin injection or saline injection for either solid or liquid emptying times. For example, liquid half emptying time was 8.2 (SD=13.7) minutes after Botox injection and 22.5 (SD=7.7) minutes after saline injection, $p>0.05$. In addition, in pooled analyses, the total GCSI score did not differ significantly after Botox compared to saline treatment (mean GCSI=6.1 and 3.8, respectively, $p>0.05$).

The other RCT, published in 2008, was a single center double-blind trial with 32 patients. Patients had symptoms consisting of delayed gastric emptying and had a GCSI score of 27 or higher. They received an



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injection of either Botox (n=16) or saline placebo (n=16). All patients completed the study. Patients were evaluated with gastric emptying scintigraphy (GES) prior to treatment and at a 1-month follow-up. The proportion of patients with at least a 9-point reduction in the GES at 1 month, the primary endpoint, was 6 of 16 (37.5%) in the Botox group and 9 of 16 (56.3%) in the placebo group; the difference between groups was not statistically significant. Improvement in gastric emptying after 1 month, a secondary endpoint, also did not differ significantly between groups. Two small RCTs have failed to show a benefit for treatment of gastroparesis. This evidence is insufficient to draw conclusions about the efficacy of botulinum toxin for this indication.

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	46505, 52287, 64611, 64612, 64613, 64615, 64616, 64617, 64640, 64642, 64643, 64644, 64645, 64646, 64647, 64650, 64653, 67345, 95873, 95874, (Code 64614 was deleted as of 1/1/2014, code 64611 added, new codes as of 1/1/2014 include 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647)



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HCPCS	J0585, J0586, J0587, J0588, S2340, S2341
ICD-9 DX	307.20 thru 307.23, 307.81, 333.0 thru 333.84, 334.1, 338.18, 338.28, 340, 341.0, 341.8, 341.9, 342.10 thru 342.12, 343.0 thru 343.9, 344.00 thru 344.9, 346.00 thru 346.93, 351.0 thru 351.9, 353.0, 355.8, 356.0, 374.87, 378.00 thru 378.9, 388.30 thru 388.32, 438.20 thru 438.7, 527.7, 530.0, 536.3, 553.3, 565.0, 595.1, 596.51, 596.54, 596.55, 600.90, 701.8, 705.21, 705.22, 719.40 thru 719.49, 723.5, 723.9, 724.2, 724.5, 726.32, 728.85, 729.1, 729.2, 751.3, 754.1, 767.8, 780.8, 781.0, 784.0, 784.49, 788.30, 788.31, 788.32, 788.33
ICD-9 PX	99.29

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11/21/2002 Medical Policy Committee review
 01/28/2003 Managed Care Advisory Council approval
 11/02/2004 Medical Director review
 11/16/2004 Medical Policy Committee review. Format revision. Clinical criteria revision.
 11/29/2004 Managed Care Advisory Council approval
 06/21/2005 Medical Policy Committee review. Policy revision; palmar hyperhidrosis added to off label uses of botulinum toxin, subject case management.
 07/15/2005 Managed Care Advisory Council approval
 02/15/2006 Medical Policy Committee review. Refer to medical director for consideration under case management was deleted.
 07/12/2006 Medical Director review
 07/19/2006 Medical Policy Committee approval. Format changes. FDA information added.
 09/06/2006 Medical Director review
 09/20/2006 Medical Policy Committee approval. Treatment of incontinence due to detrusor overreactivity caused by spinal cord injury that is inadequately controlled with anticholinergic therapy was added to the list of off-label indications that are eligible for coverage. Rationale and Source was updated to include urologic applications.
 01/17/2007 Medical Policy Committee approval. Policy format updated to reflect differentiation of botulinum toxin A and botulinum toxin B indications; coverage eligibility unchanged.
 05/02/2007 Medical Director review
 05/23/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
 05/07/2008 Medical Director review
 05/21/2008 Medical Policy Committee approval. Coverage eligibility unchanged.
 06/04/2009 Medical Director review
 06/17/2009 Medical Policy Committee approval. Added bullet to "When Services Are Eligible for Coverage" section as follows:

- 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 anticholinergic therapy.

Deleted bullet from "When Services Are Considered Investigational" section as follows:

- Detrusor overactivity not due to spinal cord injury.

Added to the existing bullet in the "When Services Are Considered Investigational" section as follows:



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	<ul style="list-style-type: none">• Detrusor sphincteric dyssynergia (after spinal cord injury)
11/12/2009	Medical Policy Committee approval.
11/18/2009	Medical Policy Implementation Committee approval. Title changed to "Botulinum Toxins" to clarify that there are several of these drugs in the policy. Deleted Botox® as a botulinum toxin Type A drug and Myobloc as a botulinum toxin Type B drug. Added Onabotulinum and Abobotulinum listed as botulinum toxin Type A drugs and Rimabotulinum listed as a botulinum toxin Type B drug.
08/05/2010	Medical Policy Committee review
08/18/2010	Medical Policy Implementation Committee approval. Added upper limb spasticity to patient selection criteria for coverage.
11/04/2010	Medical Policy Committee review
11/16/2010	Medical Policy Implementation Committee approval. Added new drug, Xeomin to policy. Format revised. New FDA approved indication for Botox for chronic migraine headaches added.
12/15/2010	Medical Policy Implementation Committee approval. Clarification of non coverage for wrinkles and cosmetic uses.
10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. Added "Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., Spinal Cord Injury, Multiple Sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication" under the FDA approved indications due to recent FDA approval.
05/03/2012	Medical Policy Committee review
05/16/2012	Medical Policy Implementation Committee approval. Added a Note to the end of the coverage section that botulinum toxins are unique, non-interchangeable and there is no fixed dose ratio among toxins. Coverage eligibility unchanged.
01/23/2013	Coding updated
02/07/2013	Medical Policy Committee review
02/20/2013	Medical Policy Implementation Committee approval. Treatment of incontinence due to detrusor overactivity was moved from off-label to labeled indications.
02/06/2014	Medical Policy Committee review
02/19/2014	Medical Policy Implementation Committee approval. Added Prevention of pain associated with breast reconstruction after mastectomy, Hirschsprung's disease, Gastroparesis, Facial wound healing, and Internal anal sphincter (IAS) achalasia to the investigational list (to track the BCBS policy). Updated background criteria for the indications that included new literature since last update or for indications deemed investigational. Also updated the references. Expanded the indications to allow for interchangeability of botulinum toxin Type A products.

Next Scheduled Review Date: 02/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. reference to federal regulations.

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- A. in accordance with nationally accepted standards of medical practice;
- B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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