Medical Policy

Subject: Botulinum Toxin
Document #: DRUG.00006
Status: Revised
Current Effective Date: 09/27/2017
Last Review Date: 08/03/2017

Description/Scope

This document addresses the use of both botulinum toxin type A (BTA) and botulinum toxin type B (BTB), including Botox® (OnabotulinumtoxinA), Myobloc® (RimabotulinumtoxinB), Dysport® (AbobotulinumtoxinA) and Xeomin® (IncobotulinumtoxinA), for the treatment of all health conditions.

Position Statement

Medically Necessary:

The use of botulinum toxin is considered **medically necessary** for strabismus.

The use of botulinum toxin is considered **medically necessary** in the treatment of the following disorders if associated with spasticity or dystonia:

- Blepharospasm
- Cerebral palsy
- Facial nerve (VII) dystonia
- Hemifacial spasm
- Hereditary spastic paraparesis
- Idiopathic torsion dystonia
- Multiple sclerosis
- Neuromyelitis optica
- Organic writer's cramp
- Orofacial dyskinesia (that is, jaw closure dystonia)
- Schilder's disease
- Spasmodic dysphonia or laryngeal dystonia (a disorder of speech due to abnormal control of the laryngeal muscles present only during the specific task of speaking)
- Spastic hemiplegia
- Spasticity related to stroke, spinal cord injury, or traumatic brain injury
- Symptomatic torsion dystonia
- Other forms of upper motor neuron spasticity

The use of botulinum toxin is considered **medically necessary** in the initial treatment of cervical dystonia (spasmodic torticollis) of moderate or greater severity when **all** of the following criteria are met:

- History of recurrent clonic or tonic involuntary contractions of one or more of the following muscles: sternocleidomastoid, splenius, trapezius or posterior cervical muscles; **and**
- Abnormal posturing, with limited range of motion in the neck, or sustained head tilt; **and**
- The duration of the condition is greater than 6 months.

Subsequent injections of botulinum toxin for the treatment of cervical dystonia (spasmodic torticollis) of moderate or greater severity are considered **medically necessary** when:

- There is a response to the initial treatment documented in the medical records; **and**
- The individual still meets the medically necessary criteria above.

The use of botulinum toxin is considered **medically necessary** in the treatment of achalasia.

The use of botulinum toxin is considered **medically necessary** in the treatment of anal fissures.

The use of botulinum toxin is considered **medically necessary** in the treatment of significant drooling in individuals who are unable to tolerate scopolamine.

The use of botulinum toxin is considered **medically necessary** as a treatment of neurogenic overactive bladder (also referred to as detrusor overactivity or detrusor sphincter dyssynergia) that is inadequately controlled with anticholinergic therapy.

The use of botulinum toxin is considered **medically necessary** as a treatment of idiopathic overactive bladder in adults who are unresponsive to or intolerant of a trial of anticholinergic therapy.

The use of botulinum toxin is considered **medically necessary** for the treatment of functional obstruction caused by the inability of the internal anal sphincter to relax in individuals with Hirschsprung disease who have undergone prior surgical treatment.

An initial 6 month trial of botulinum toxin for prevention of chronic migraine headaches is considered **medically necessary** when **all** of the following are met:

- Adult individual diagnosed with chronic migraine headache; **and**
- Fifteen (15) or more headache-days per month with headache lasting 4 hours or longer; **and**
- First episode at least 6 months ago; **and**

- Symptoms persist despite trials of at least one agent in any two of the following classes of medications used to prevent migraines or reduce migraine frequency:
    - Antidepressants (for example, amitriptyline, nortriptyline, doxepin); **or**
    - Antihypertensives (for example, propranolol, timolol); **or**
    - Antiepileptics (for example, valproate, topiramate, gabapentin).

Continuing treatment with botulinum toxin injection for ongoing prevention of chronic migraine headaches is considered medically necessary for individuals who have previously met criteria above and completed an initial 6-month trial when:

- Migraine headache frequency was reduced by at least 7 days per month (when compared to pre-treatment average) by the end of the initial trial; **or**
- Migraine headache duration was reduced by at least 100 total hours per month (when compared to the pre-treatment average) by the end of the initial trial.

The use of botulinum toxin is considered **medically necessary** for the treatment of *primary* hyperhidrosis for those individuals who have failed a 6-month trial of any one or more types of nonsurgical treatment (for example, topical dermatologics such as aluminum chloride, tannic acid, glutaraldehyde or anticholinergics, systemic anticholinergics, tranquilizers or non-steroid anti-inflammatory drugs) and meet any ONE of the following criteria:

- Presence of medical complications or skin maceration with secondary infection; **or**
- Significant functional impairment, as documented in the medical record.

The use of botulinum toxin is considered **medically necessary** for the treatment of *secondary* hyperhidrosis when the condition is related to surgical complications and both of the following criteria are met:

- Presence of medical complications or skin maceration with secondary infection; **and**
- Significant functional impairment, as documented in the medical record

Not Medically Necessary:

The use of botulinum toxin is considered **not medically necessary** in the treatment of cervical dystonia (spasmodic torticollis) when the criteria above have not been met.

The use of botulinum toxin is considered **not medically necessary** for the treatment of primary or secondary hyperhidrosis when the criteria above have not been met.

Cosmetic and Not Medically Necessary:

Botulinum toxin is considered **cosmetic and not medically necessary** as a treatment of skin wrinkles or other cosmetic indications.

Investigational and Not Medically Necessary:

Botulinum toxin is considered **investigational and not medically necessary** for the treatment of headache other than chronic migraine meeting the criteria above, including but not limited to tension, episodic migraine (14 migraine days per month or less), or chronic daily headaches.

The use of botulinum toxin is considered **investigational and not medically necessary** for the treatment of individuals with Hirschsprung disease when the criteria above are not met.

The use of botulinum toxin, whether the same or a different product, following failure of an initial trial for the treatment of a medically necessary condition (as listed above) is considered **investigational and not medically necessary. Note:** when the initial product was stopped due to a product specific intolerance or allergic reaction (rather than clinical failure), this investigational and not medically necessary statement does not apply.

Botulinum toxin is considered **investigational and not medically necessary** as a treatment for conditions listed above when criteria are not met and for all other conditions not addressed above, including, but not limited to, the following:

- Anismus (pelvic floor dyssynergia)
- Behcet's syndrome
- Benign prostatic hyperplasia
- Brachial plexus palsy
- Carpal tunnel syndrome
- Chronic motor tic disorder
- Disorders of the esophagus (except as listed above in the medically necessary section)
- Epicondylitis
- Fibromyalgia/fibromyositis
- Gastroparesis
- Low back pain
- Myofascial pain syndrome
- Neck pain not related to conditions mentioned above
- Nystagmus
- Parkinson's disease
- Post-mastectomy reconstruction syndrome
- Reynaud's syndrome
- Sphincter of Oddi dysfunction
- Stuttering
- Tics associated with Tourette's Syndrome
- Tinnitus
- Tourette's Syndrome
- Tremors
- Urinary and anal sphincter dysfunction (except as listed above in the medically necessary section)
- Vaginismus

- Whiplash-related disorders
- Zygomatic fractures

Clinically Equivalent Cost Effective Agents

Note: When botulinum toxin is determined to be medically necessary based on the clinical criteria above, the benefit plan may have in addition a medically necessary criterion that the treatment be cost effective.

A benefit plan may select any one or more of the following as clinically equivalent cost effective botulinum toxin agents: Botox (OnabotulinumtoxinA), Myobloc (RimabotulinumtoxinB), Dysport (AbobotulinumtoxinA) and Xeomin (IncobotulinumtoxinA). A list of one or more cost effective botulinum toxin agents for each plan is available here.

In benefit plans where there is a requirement to use a cost effective botulinum toxin agent, requests for a botulinum toxin agent that is not cost effective may be approved when the following criteria are met:

A. The individual has had a trial of and is intolerant to one cost effective agent; **or**
B. For the prescribed indication, the cost effective agent(s) is/are not FDA-approved or does not meet the off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use (see below) **and** there is documentation that the cost effective agent(s) is/are not clinically appropriate due to agent potency, technical administration and/or dosing; **or**
C. The cost effective agent is not acceptable due to the following concomitant clinical situation(s):
    1. Dysport (abobotulinumtoxinA) is designated as the sole cost effective agent and the individual has a known hypersensitivity to cow's milk protein*.

***Note:** Dysport contains lactose as an inactive ingredient. Individuals with a severe milk protein allergy should avoid use due to the risk of anaphylactic reactions.

FDA-approved Indications or Indications Meeting off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use

	Dysport (AbobotulinumA)	Xeomin (IncobotulinumtoxinA)	Botox (OnabotulinumtoxinA)	Myobloc (RimabotulinumtoxinB)
Achalasia			Y	
Blepharospasm in adults	Y	X	X	Y
Blepharospasm in children	Y	Y	X	Y
Cervical dystonia	X	X	X	X
Chronic anal fissure			Y	
Cranial-cervical dystonias			Y	
Difficulty speaking – Total laryngectomy			Y	
Disorder of esophagus			Y	
Excessive salivation			Y	Y
Hemifacial spasm	Y		Y	Y
Hyperhidrosis			X	Y
Incontinence- Spinal cord injury				Y
Isolated oromandibular dystonia			Y	
Lower limb spasticity in children 2 years of age and older	X			
Lower limb spasticity in adults	X		X	

Meige's syndrome (idiopathic blepharospasm)			Y	
Migraine prophylaxis			X	Y
Organic voice tremor			Y	
Oromandibular dystonias			Y	
Overactive bladder			X	Y
Pelvic floor dyssynergia			Y	
Spasm of pharyngoesophageal segment – Total laryngectomy			Y	
Spasmodic dysphonia			Y	Y
Spasticity related to cerebral palsy			Y	
Strabismus for 12 years of age and older			X	
Upper limb spasticity	X	X	X	Y
Urinary incontinence			X	

X = FDA-approved Indications (excluding cosmetic indications)
Y = Indications Meeting off-label drug use criteria of CG-DRUG-01 Off-Label Drug and Approved Orphan Drug Use

Rationale

Achalasia

Achalasia is a primary esophageal motor disorder characterized by abnormal lower esophageal sphincter relaxation. The available literature addressing the use of botulinum toxin for achalasia is currently limited to a few studies, including a single case report (Perez-Arroyo, 1997), a retrospective case series of 5 subjects (Ahsan, 2000), and several small prospective case series studies (Alberty, 2000; Annese, 1998; Miller, 1996; Storr, 2001). These small studies show some benefit. Data from two small randomized controlled trials are available for individuals with achalasia.

Mikaeli and colleagues (2006) randomly assigned newly diagnosed individuals with achalasia to receive botulinum toxin 1 month before pneumatic dilatation (n=27) or to undergo pneumatic dilatation alone (n=27). At 1 year, the remission rate in the botulinum toxin-pneumatic dilatation group was 77% compared with 62% in pneumatic dilatation group ($p=0.1$). In the pneumatic dilatation group, the esophageal barium volume significantly ($p<0.001$) decreased at 1 month, but this reduction did not persist over 1 year follow-up. The botulinum toxin-pneumatic dilatation group showed a significant ($p<0.001$) reduction in barium volume at the various time intervals post-treatment. In the botulinum toxin-pneumatic dilatation group, 10/11 (91%) subjects over 40 were in remission at 1 year, compared with only 5 of 9 (55%) cases in the pneumatic dilatation group ($p=0.07$).

Anal Fissure

An anal fissure is a tear in the lower half of the anal canal that is maintained by contraction of the internal anal sphincter. It is treated surgically with an internal sphincterotomy. Since the anal sphincter contraction could be characterized as a dystonia, botulinum toxin represented a logical medical approach. Maria and colleagues (1998) reported on a randomized study of 30 individuals with chronic anal fissure who received either two injections of 20 units of botulinum toxin, on either side of the fissure, or two injections of saline. After 2 months, 11 subjects in the treatment group reported healing, compared to only 2 in the control group. The 4 participants who still had fissures after 2 months underwent retreatment with botulinum toxin; 2 of these 4 individuals reported healing scars and symptomatic relief. These results are consistent with earlier case series that reported a healing rate of 80% (Jost, 1997). Nitroglycerin ointment has also been used to successfully treat anal fissure. Brisinda and colleagues (1999) compared the results of nitroglycerin ointment and botulinum toxin in a randomized trial of 50 subjects. After 2 months, 96% of the fissures were healed in the botulinum group compared with 60% in the nitroglycerin group.

In 2017, the American Society of Colon and Rectal surgeons published a new Practice guideline for the management of anal fissures (Stewart, 2017). Their recommendation addressing the use of botulinum toxin states, "Botulinum toxin has similar results compared with topical therapies as first-line therapy for chronic anal fissures, and modest improvement in healing rates as second-line therapy following treatment with topical therapies."

Benign Prostatic Hyperplasia (BPH)

Botulinum toxin has been investigated for the treatment of urinary symptoms of benign prostatic hyperplasia (BPH). At

this time, the peer-reviewed published literature for this treatment method is limited. One study by Maria and colleagues (2003) involved 30 consecutive male individuals with BPH enrolled in a randomized controlled trial. Each participant received 4 mL of either saline solution or 200 U of botulinum toxin A injected into the prostate gland. After 2 months, 13 participants in the treated group and 3 in the control group had subjective symptomatic relief (p=0.0007). In individuals who received botulinum toxin, the symptom score was reduced by 65% compared with baseline values and the serum prostate-specific antigen concentration by 51% from baseline. In subjects who received saline, the symptom score and serum prostate-specific antigen concentration were not significantly changed compared with the baseline values and 1 month values. Follow-up averaged 19.6 ± 3.8 months. Another study by Park et al. (2006) included 52 individuals with symptomatic BPH who received either transperineal intraprostatic injection with botulinum toxin A (BT group) or botulinum toxin A with additional alpha-adrenergic antagonist therapy (Btalpha group). Twenty-six individuals were in the BT group and 26 were in the Btalpha group. At the 1 month follow-up, 18 subjects in the BT group and 21 in the Btalpha group had subjective symptomatic relief (p=0.337). Only international prostate symptom score 5 (weak stream) was significantly different between the BT group and Btalpha group (p=0.034). At the 3-month follow-up, 39 participants had subjective symptomatic relief. The storage symptoms were improved more than the voiding symptoms. Additionally, about 50% of the subjects whose voiding symptoms improved expressed improved erectile function. BTA injection seems to be an alternative treatment for BPH. The differences after the 1-month evaluation between the BT and the Btalpha groups might suggest that the adrenergic influence could be relatively reinforced by the anticholinergic effect of BTA.

Marberger and colleagues (2013) published the results of a double-blind randomized controlled trial (RCT) involving 380 subjects with BPH treated with a single transperineal (n=63) or transrectal (n=311) injection of BTA (n=286) vs. placebo injection (n=94). The BTA groups were randomly assigned to receive treatment with either 100 U (n=95), 200 U (n=94), or 300 U (n=97). The results indicated that there were no significant differences between any of the BTA groups vs. placebo at 12 weeks with regard to International Prostate Symptom score, maximum flow rate, total prostate volume, or transitional zone volume.

A randomized placebo-controlled trial involved 315 subjects with BPH assigned to either 200 U of Botox (n=157) or placebo (n=156; McVary, 2014). Subjects were followed for 24 weeks and evaluated with the International Prostate Symptom Score tool and peak urinary flow. The authors reported no significant overall differences between groups, indicating a lack of efficacy of Botox for BPH.

At this time, the current data does not allow for a sufficient evaluation of botulinum toxin for the treatment of BPH.

Brachial Plexus Palsy

Botulinum toxin has been investigated as a treatment of brachial plexus palsy. At this time, there are no RCTs published addressing this treatment method. The body of literature is composed of case series studies of varying sizes involving subjects with birth-related brachial plexus injuries. The largest of these was published by Immerman in 2013. This study involved 71 consecutive subjects who underwent subscapularis slide correction involving botulinum toxin, who were available for evaluation at 2 years post-procedure. In this study, botulinum toxin was used as an adjunct to five different surgical techniques, which were the focus of the study. The authors reported successful outcomes with all techniques, but no data is presented to specifically address the role of botulinum toxin. The next largest study was a retrospective case series reported by Michaud and colleagues (2014). This study involved 59 subjects who, while under local or general anesthesia, received injections of botulinum toxin A (5 U per 0.1 mL or 10 U per 0.1 mL, depending upon injection site) from a single investigator. The number of injections varied depending on clinical needs, but was generally between 4 to 5 in each of the shoulder and elbow muscles, and single injections into the pronator teres, biceps and triceps in approximately equal volumes per injection. Injection was followed by physical and occupational therapy. The authors reported that 10 subjects underwent one repeat treatment and 2 others underwent two additional treatments. The authors reported that for subjects who received shoulder injections (n=51), global average active and passive shoulder external rotation (SER) improved in 35.5% of subjects and total Mallet component shoulder scores increased 55% during the time period within which the botulinum toxin was effective (between 1 and 6 months post-treatment). For the same population, total Mallet component shoulder scores were improved in 68.8% of subjects when compared to baseline during the period after treatment when the effects of botulinum toxin were no longer active (BNA, range 7-43 months). SER scores were not different between baseline and BNA. In this population, surgery was reportedly averted, modified or deferred in 45% of subjects who were under consideration for surgery prior to botulinum treatment. Triceps injections were done in 15 subjects. During the active botulinum toxin period, total Toronto scores improved in 66% of subjects. During BNA, elbow flexion and Toronto scores improved from baseline in 100% of evaluable subjects (9/15). Surgery was averted in 2 of the 7 subjects in this population for whom surgery was a consideration. Pronator teres was injected in 15 subjects and active supination was noted in 77.3% (p=0.001) during the active botulinum toxin period. These gains were maintained or improved in 53.5% of subjects during BNA (p=0.016). Injections into the biceps were completed in 9 subjects, and average passive elbow extension was significantly improved by 17% (p=0.04). During the active botulinum period, an average of 49% gain in passive range of motion in elbow extension was seen, but these gains were not continued into the BNA. No significant changes in the total Toronto and elbow extension component scores were noted at any time point.

Additional data are available from several other studies (De Matteo, 2006; Ezaki, 2010; Price, 2007; Rollnik, 2000). However, these case series studies have very small subject pools (n=8, 35, 13, and 6, respectively). These studies also reported beneficial results from Botulinum toxin injections for the treatment of brachial plexus palsy. However, the findings reported by these studies, as well as those by Immenman and Michaud, while promising, are derived from studies of poor quality. Lack of a comparison group, small study populations, and other factors hamper the generalizability to the results to wider clinical practice.

Drooling

Botulinum toxin has been investigated as a treatment of significant drooling, primarily in participants with Parkinson's disease or cerebral palsy. Several randomized controlled trials have demonstrated botulinum toxin can decrease the volume of saliva compared to placebo, as evidenced by a change in the number of bibs required each day (Lipp, 2003; Mancini, 2003; Ondo, 2004). However, oral scopolamine is an effective technique of reducing salivary flow. One study randomized 45 children with cerebral palsy to receive either scopolamine therapy or injections of botulinum toxin (Jongerius, 2004). No significant differences in reduction in saliva volume were noted between the two groups, although those receiving scopolamine had greater side effects. The results of this study suggest that botulinum injection is a

reasonable alternative for those who cannot tolerate scopolamine.

Epicondylitis

At this time, there are several randomized controlled trials describing the effectiveness of botulinum toxin therapy for epicondylitis (Espandar, 2010; Hayton, 2005; Keizer, 2002; Placzek, 2007; Wong, 2005). The studies reported by Hayton (n=40), Wong (n=60) and Placzek (n=130) described trials where botulinum toxin A was compared to saline placebo injections. None of these studies reported significant differences in objective measures at 12 and 18 weeks post-treatment, respectively. Espandar and colleagues also compared botulinum toxin to saline placebo injections in 48 subjects with epicondylitis, but found significant decrease in pain at rest for the botulinum toxin group during the follow-up period. No other measures were found to be significantly different between groups. The trial by Keizer (n=40) compared botulinum toxin A injection to surgery. The authors reported that when analyzed with an overall scoring system, no differences were found between the two forms of treatment after 3, 6, 12, and 24 months. A meta-analysis by Kalichman and others combined and analyzed data from the Espandar, Hayton, Placzek and Wong studies (2011). The authors report that the summary data "showed a moderate effect for pain favoring botulinum toxin." However, no p-value is provided for this data, so it is unclear whether or not this effect was statistically significant. Data from larger randomized trials are needed to confirm these findings.

Gastroparesis

Botulinum toxin has been researched as a treatment of gastroparesis. Through upper endoscopy, botulinum toxin has been injected into the pylorus to relax the muscle and speed emptying of gastric contents. The literature consists of several small studies ranging in size from 3 to 60 individuals. Although the results show some positive effect after treatment with botulinum toxin, larger controlled trials are needed to determine the efficacy of this treatment method for gastroparesis (Arts, 2007; Bagheri, 2013; Friedenberg, 2004, 2008). The current version of the American College of Gastroenterology clinical guidelines for the treatment of Gastroparesis (2013) states, that "…botulinum toxin injection into the pylorus is not recommended as a treatment for gastroparesis, although there is a need for further study in patients with documented 'pylorospasm.'"

Headaches

Numerous studies regarding the treatment of migraine, tension, and cluster headaches have been published (Evers, 2004; Freitag, 2008; Khalil, 2014; Ondo, 2004; Padberg, 2004; Petri, 2009; Relja, 2004; Rollnik, 2000; Rollnik, 2004; Saper, 2007; Schmitt, 2001; Schulte-Mattler, 2004; Silberstein, 2000; Smuts, 1999). Silberstein (2005) published a large randomized, double-blind, placebo-controlled study addressing the use of botulinum toxin for chronic migraine headaches involving 702 subjects. This study compared placebo to three different concentrations of botulinum toxin. Mathew and colleagues (2005) studied 355 participants with chronic daily headache who were categorized as placebo responders or non-responders based on an initial single-blind trial of placebo. Both placebo responders and non-responders were then randomized to receive either placebo or botulinum toxin every 90 days for 9 months; individuals were evaluated every 30 days. In both studies, there was no statistically significant difference in the primary outcome, although there were several statistically significant differences in some of the secondary outcomes. Anand and colleagues (2006) studied 32 individuals receiving pericranial botulinum toxin injections for multiple monthly migraines. They reported 75% of the subjects had some relief from migraine pain, but still had migraine-associated decreased normal daily functioning. Relja and colleagues published the findings of a large double-blind, placebo-controlled study which involved 495 participants (2007). The study evaluated the efficacy of three concentrations of botulinum toxin compared to placebo for the treatment of chronic migraine headaches. The authors reported no significant differences between any of the experimental groups and placebo for the primary efficacy endpoint, which was the mean reduction from baseline in the frequency of migraine episodes at day 180 in the placebo non-responder stratum. These publications demonstrate the challenges in studying interventions to treat chronic migraine and the inconsistent and often conflicting results were not sufficient to convincingly demonstrate medical benefit of botulinum toxin in migraine.

However, more recently, Dodick and colleagues reported the pooled results of two large randomized, double-blind, controlled trials addressing the use of botulinum toxin for the treatment of chronic migraine headaches (2010). These studies, from the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program, involved a 24-week randomized, double-blind phase followed by a 32-week open-label phase (Aurora, 2010; Diener, 2010). Subjects were randomized (1:1) to onabotulinumtoxinA or placebo injections every 12 weeks. A total of 1384 adults were randomized to onabotulinumtoxinA (n=688) or placebo (n=696). Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favoring onabotulinumtoxinA over placebo at week 24 (-8.4 vs. -6.6; $p<0.001$) and at all other time points. Significant differences favoring onabotulinumtoxinA were also observed for all secondary efficacy variables at all time points, including frequency of headache days, cumulative headache hours, and the proportion of subjects with severe headaches. No significant difference was noted in the frequency of acute headache pain medication taken. There were a significantly greater proportion of experimental group subjects that had a greater that 50% decrease from baseline in headache days. Adverse events occurred in 62.4% of experimental group subjects and 51.7% of placebo subjects, with a greater than 5% incidence of neck pain and muscular weakness in the experimental group.

Based in part on the Dodick study, in October 2010 the U.S. Food and Drug Administration (FDA) approved the use of onabotulinumtoxinA (Botox) for the prophylaxis of headaches in adults with chronic migraine as defined as greater than or equal to 15 days per month with headache lasting 4 hours a day or longer. This approval appears to recognize that taken in aggregate, the published peer-reviewed evidence supports that the use of botulinum toxin demonstrates material improvements in net health outcomes, in particular a reduction in migraine frequency in carefully selected individuals.

A report by Lipton and colleagues looks further into these results, with an analysis of combined data from both the PREEMPT-1 and PREEMPT-2 trials. This report, which looked at 688 subjects who received treatment with Botox vs. 696 who received saline placebo injections, showed that while both groups demonstrated significant improvement, the Botox group had significantly better overall HIT-6 scores at all time periods during the double-blind phase of the trials ($p\leq0.014$). Additionally, HIT-6 measures of headache impact scores showed significant benefit for the Botox group at 24 weeks of treatment ($p<0.001$). Finally, there was a significant benefit shown for the Botox group compared to placebo with regard to the proportion of subjects who received clinically meaningful reduction in the number of headache days at all time points in the double-blind study periods ($p\leq0.025$). These results further support the findings of the individual

PREEMPT studies, and demonstrate a significant benefit from Botox treatment for chronic migraine headache sufferers.

In 2014, Aurora and others published a secondary analysis of data from all subjects from both the PREEMPT-1 and PREEMPT-2 trials that completed all 5 cycles of treatment. Out of a total of 1384 subjects from both studies, 1005 were included in this report. Of these, 513 received all 5 cycles with BTA, whereas 492 underwent 2 cycles of placebo followed by 3 cycles of BTA treatment. At the end of 56 weeks of treatment, significant benefits were found for BTA treatment vs. placebo with regard to mean change in the frequency of headache days (p=0.035), total migraine days (p=0.038), and moderate/severe headache days (n=0.042). Treatment-related adverse event rates were 28.5% for the BTA group vs. 12.4% for the placebo group during the double-blind phase of the trials. The most frequently reported treatment related adverse events were neck pain (4.3%), muscular weakness (1.6%), injection site pain (2.1%), and eyelid ptosis (1.9%). This data continues to support the use of BTA for the treatment of migraine headaches.

A double-blind RCT of BTA for the treatment of tension-type headaches was reported by Silberstein (2006). The study included 300 subjects who were randomized to receive treatment with either BTA injections into 5 pre-specified sites; BTA in 3 of the sites; and placebo into the other 2 sites (Usub group); or placebo in all 5 sites. Doses were BTA 150 U (n=49), BTA 100 U (n=51), BTA 100 Usub (n=52), BTA 86 Usub (n=51), BTA 50 U (n=47), or placebo (n=50). For the primary endpoint, the mean change from baseline in the number of tension-type headache-free days per month, there was no statistically significant difference between placebo and four BTA groups. However, a significant difference favoring placebo vs. BTA 150 was observed (4.5 vs. 2.8 tension headache-free days/month; p=0.007). This study indicates a lack of efficacy of BTA treatment for tension-type headaches.

The diagnosis and classification of headaches can be challenging. The International Headache Society published the International Classification of Headache Disorders, Second Edition (ICHD-II, 1st Revision) in May, 2005. This document, used primarily for research purposes, provides specific criteria for the identification and classification of chronic migraine headache. The criteria for chronic migraine headache are:

A. Headache fulfilling criteria C and D below on ≥ 15 days per month for greater than 3 months
B. Headache is not attributable to another disorder
C. Headache has at least two of the following characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia

Hirschsprung disease

The use of botulinum toxin has been proposed for the treatment of functional obstruction caused by the inability of the internal anal sphincter to relax in individuals with Hirschsprung disease who have undergone prior surgical treatment; however, it has not been widely investigated. A nonrelaxing internal anal sphincter is present in a number of children with surgically treated Hirschsprung disease and can cause obstructive gastrointestinal symptoms. It has been hypothesized that intrasphincteric injections of botulinum toxin may relieve muscle contractility in these individuals, with the ultimate goal of preventing complications and the need for further interventions, including surgery. At this time, the body of evidence addressing this condition is limited to small case series studies, which are mostly retrospective record reviews. The largest available study involved 33 children with Hirschsprung disease-related distal bowel obstruction who had undergone previous surgical interventions who were treated with Dysport (Han-Geurts, 2014). The median follow-up time was 7.3 years and short-term improvement was reported for 76% of subjects. No response to a first treatment was seen in 7 subjects, although 2 of these responded favorably to subsequent injections. Hospitalizations for enterocolitis decreased from 19 subjects to 7 subjects post-injection. Overall, a good response was reported in 49% of subjects with no significant complications related to the injections reported. Similar results have been reported in the other small studies, including those involving subjects following unsuccessful pull-through surgery (Basson, 2014; Hukkinen, 2014; Koivusalo, 2009; Minkes, 2000; Patrus, 2014; Wester, 2015). Despite the low strength of this evidence, the use of intrasphincteric injections of botulinum toxin has become accepted as a treatment of last resort for individuals with this rare condition and rare complication. Continued investigation into this treatment method would be helpful to further understand its efficacy and safety for both this and other clinical situations related to Hirschsprung disease.

Hyperhidrosis

Botulinum toxin has been widely recognized as a safe and effective method of treatment for primary hyperhidrosis when conservative treatments have failed, and for secondary hyperhidrosis when related to surgical complications. Multiple studies have demonstrated long-term symptom relief from these conditions due to botulinum toxin injections (Lowe, 2002, 2007; Naumann, 2001, 2002, 2003; Naver, 2002; and Shelley, 1998).

Low Back Pain

Foster et al. (2001) reported on a randomized double-blind study of botulinum toxin A in 31 consecutive subjects with chronic low back pain. Study selection criteria included low back pain of at least 6 months duration with more predominant pain on one side. Subjects were excluded if there was a systemic inflammatory disorder, acute pathology on MRI, or involvement in worker's compensation or litigation among other criteria.

The outcome measures used in this study were a visual analogue scale (VAS) for pain, measured at baseline, 3 weeks and 8 weeks; a 50% reduction was considered a response. The Oswestry Low Back Pain Questionnaire (OLBPQ) was used to measure functional ability at baseline and at 8 weeks. This measure has 10 different subscales (pain, personal care, lifting, walking, sitting, standing, sleeping, sex, social life, and traveling) each rated 0 to 5. Responders were required to show a 2-point reduction on the pain subscore and on at least 1 of the other subscales. Three subjects withdrew or were lost to follow-up over the course of the 8-week study, and these subjects were included in the intent-to-treat analysis as non-responders. Subjects were injected with 40 units of Botox (Allergan, Inc.) at five lumbosacral locations for a total of 200 U (treated group) or saline placebo (placebo group). Injections were made on one side of the back only, depending on predominance of pain.

At baseline, pain scores on the VAS in the treated group ranged from 6 to 10, with an average of 7.5; in the placebo group, scores ranged from 5 to 10, with an average of 7. At 3 weeks, 73.3% of treated subjects and 25% of the placebo group showed a response on VAS scores (p=0.012). This difference in VAS scores remained significant at 8 weeks with 60% of treated subjects and 12.5% of placebo subjects still responding (p=0.009). The OLBPQ assessment at 8 weeks showed that 66.7% of treated subjects and 18.8% of placebo subjects were responders (p=0.011). These results show clinically significant and statistically significant improvements in treated subjects as compared with placebo on all three outcome assessments.

However, this is only one suggestive study that included 31 subjects, and replication of these findings would be desirable. The population with chronic low back pain is a heterogeneous population, and results in this small group of selected subjects cannot be used to generalize results for the whole population with chronic low back pain. Furthermore, studies should examine the long-term effectiveness of using repeated courses of botulinum toxin to determine the durability of repeated treatments.

Myofascial Pain

Painful muscles with increased tone and stiffness containing trigger points characterize myofascial pain syndrome. Subjects 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. Among three studies on cervicothoracic myofascial pain syndrome, Wheeler and colleagues (1998) conducted a randomized trial of 33 subjects randomized into three groups; one group receiving 50 units of botulinum toxin, one group receiving 100 units of botulinum toxin, and one group receiving normal saline. All three groups showed similarly significant treatment effects, based on the Neck Pain and Disability Visual Analogue Scale. These same authors (Wheeler, 2001) later found no differences among 50 subjects randomized to high-dose botulinum toxin or placebo. A crossover study of only 6 subjects (Cheshire, 1994) found significantly better results for botulinum toxin over placebo at 2 and 4 weeks for 4 of 5 pain outcomes. Together, these three studies are insufficient to permit conclusions about the effects of botulinum toxin on cervicothoracic myofascial pain syndrome.

A study by Nicol (2014) enrolled 114 subjects with cervical and shoulder girdle myofascial pain to receive one injection of botulinum toxin A into painful muscle groups. Responders of this initial treatment (n=54) were then enrolled in a randomized placebo-controlled trial where subjects received another set of injections with either botulinum toxin A or saline and followed for 12 weeks. Significant improvements were reported in the botulinum toxin A group vs. placebo with regard to visual analog pain scales (p=0.019), headaches per week (p=0.04), and Brief Pain inventory scales for general activity and sleep (p=0.0.46 and p=0.02). This study indicates that botulinum toxin A may provide significant role in the treatment of select individuals with cervical and shoulder myofascial pain. Further studies with larger populations are warranted to support these findings.

Three studies addressed another form of myofascial pain, piriformis syndrome, characterized by buttock tenderness and sciatica. One very small study of 9 subjects (Childers, 2002) compared botulinum toxin with placebo, finding post-injection pain scores were significantly improved in the treatment group for only 1 of 4 pain domains, while none improved in the placebo group. Unfortunately, the small sample size and lack of control group significantly limits the usefulness of these findings. Another study of 36 subjects (Fishman, 2002) found that the group given botulinum toxin had a 50% or greater reduction in pain on each of the last two follow-up visits, compared with lidocaine and steroid injections. This study had a significantly high loss to follow-up (35.6%), with statistically significant difference in the proportion of participants dropping out in each group. These small and flawed studies do not establish that the effects of botulinum toxin exceed those of placebo. A third study (Porta, 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.

Nystagmus

The available evidence addressing the use of botulinum toxin for the treatment of nystagmus is limited to two small case series studies. Tomsak and colleagues (1995) report on 3 subjects with acquired nystagmus with prominent vertical or torsional components. Each subject received a different concentration of botulinum toxin A (10, 12.5, or 25 units) via retrobulbar injection. The authors report that botulinum toxin abolished or reduced all components of the nystagmus in the treated eye in all 3 subjects for about 2 to 3 months. The subject who received 25 units developed complete external ophthalmoplegia and blepharoptosis. The other 2 subjects retained some voluntary movements but developed diplopia. In 1 subject, visual acuity improved from Jaeger 5 to Jaeger 1. In a second subject, filamentary keratitis developed, and visual acuity declined from Jaeger 2 to Jaeger 7; keratitis was a recurrent problem 1 year after the botulinum toxin injection. In the third subject with predominantly torsional nystagmus, visual acuity was unchanged at Jaeger 2. No subject was pleased with the results, because of blepharoptosis, diplopia, or discomfort (from keratitis), and none elected to repeat the procedure.

The other study by Repka et al. (1994) was a prospective study of 6 subjects (9 eyes) with acquired nystagmus. The subjects received retrobulbar injection of 25 to 30 U of botulinum neurotoxin A. Subjects were followed for changes in their visual function for at least 6 months following the last injection. Each subject had subjective and objective improvement in distance visual acuity following the injection. A reduction in the amplitude of the nystagmus was seen following each of the injections, but the frequency of the nystagmus was generally unchanged. Visual improvement usually lasted no more than 8 weeks. However, improvement persisted for 6 months after injection in 2 subjects with oculopalatal myoclonus.

These two studies are insufficient to establish the efficacy and safety of the use of botulinum toxin for the treatment of nystagmus.

Spasticity and Dystonia

The use of botulinum toxin therapy is a well-established, safe and effective treatment for a variety of spasticity related disorders and abnormal muscle tone, including muscle over-activity or spasticity related to upper motor neuron (UMN) syndrome caused by cerebral palsy, multiple sclerosis, stroke, spinal cord injury, or neurodegenerative disease. Controlled clinical trials of botulinum toxin injections for focal muscle spasticity have demonstrated prolonged yet reversible clinical improvements in physical function and comfort, as well as improvement in prevention or treatment of

musculoskeletal complications. These benefits have been achieved with few side effects.

Botulinum toxin treatment has been demonstrated to be a safe and effective method for decreasing the severity of abnormal head positioning and postures and pain associated with various dystonias such as cervical, spasmodic, and torsion dystonia. Although botulinum toxin therapy has not resulted in complete relief of symptoms for these conditions, clinical trials have demonstrated temporary but significant improvements in the degree of muscle contractility, flexibility, and pain. An added benefit of this treatment is the ability to target specific muscles in a dose-response relationship, allowing a precise amount of muscle weakness to be induced.

Spasticity related to stroke may be a significant functional problem. Plantar flexion spasticity may impede walking. Peripheral neurolysis with phenol injections has been used for many years, but recently botulinum toxin injections have been investigated. Kirazli and colleagues (1998) compared the effects of phenol block and botulinum toxin in a randomized trial of 20 subjects with spastic foot after stroke. The authors reported both injections were associated with significant improvements, with botulinum toxin outperforming phenol injections after the first month of treatment, with equal treatment effects at 2 and 3 months. A possible advantage of the botulinum toxin is the relative ease of the procedure (15 to 30 minutes), while phenol injection may take up to 2 hours to target the motor nerve for injection. Smith and colleagues (2000) investigated the use of botulinum toxin in a trial which randomized 21 individuals with upper limb spasticity related to stroke or head injury. There was a significant reduction in spasticity in the wrist and fingers in the botulinum group. The effects were transitory and disappeared at 12 weeks. This same population was studied by Rosales and others in 2012. In their randomized placebo-controlled study, 163 subjects were assigned to receive treatment with either Dysport (n=80) or placebo (n=83). The authors report that results of Modified Ashworth Scale (MAS) were significantly better in the Dysport group vs. controls at all time points up to the 24-week follow-up ($p<0.001$). No significant difference in adverse events was reported.

A meta-analysis of botulinum toxin for the treatment of upper limb function was reported by Foley in 2013. The study inclusion criteria used were (1) the study was a randomized controlled trial (RCT); (2) the sample was composed of subjects > 18 years old of whom at least 60% were recovering from either first or subsequent stroke, presenting with moderate to severe spastic upper-limb hemiplegia; (3) subjects who received an injection of botulinum toxin type A (BTA) to muscles in the shoulder, elbow, wrist, or fingers were compared with those who had received a placebo or nonpharmacologic treatment; and (4) an assessment of activity performance or capacity was made. A total of 10 studies met inclusion criteria and also reported sufficient data for inclusion in the pooled analysis (n=1000). Two of the studies fulfilled all three criteria for methodologic quality. A third study included a no-treatment control group, and was only single-blind, but met the other two criteria. Among the remaining studies, one study did not fulfill any of the three criteria, nine studies were double-blind only, and three studies were both double-blind and performed an intention-to-treat analysis. Six different outcomes that assessed activity limitations had been used, including the Disability Assessment Scale, the Action Research Arm Test, and the Barthel Index. Overall, the authors reported that BTA was associated with a moderate treatment effect (standardized mean difference 0.536 ± 0.094, 95% confidence interval [CI], 0.352-0.721; $p<0.0001$). This analysis provides some good data on the use of BTA for the use of stroke-related conditions. However, it also points out significant weaknesses in the overall state of the available evidence addressing this treatment method.

In 2016, Elovic and others reported the results of an RCT involving 259 subjects with post-stroke upper limb spasticity assigned in a 2:1 fashion to treatment with incobotulinumtoxinA (fixed dose 400 U, n=171) or placebo (n=88). At week 4, the authors reported that incobotulinumtoxinA led to larger improvements in primary target clinical pattern (PTCP) Ashworth scale (AS) scores than placebo ($p<0.001$). More subjects were PTCP AS responders (≥ 1-point improvement) with incobotulinumtoxinA than with placebo (69.6% vs. 37.5%, respectively $p<0.001$). Investigator's Global Impression of Change confirmed superiority of incobotulinumtoxinA vs. placebo ($p=0.003$). Adverse events were mainly mild/moderate, and were reported by 22.4% (incobotulinumtoxinA) and 16.8% (placebo) of subjects. They concluded that incobotulinumtoxinA significantly improved upper-limb spasticity and associated disability, and was well-tolerated.

Sphincter of Oddi dysfunction

To date, only two studies have investigated the use of botulinum toxin for the treatment of sphincter of Oddi dysfunction. Both case series studies are by the same group of authors, Wehrmann and colleagues. The first study (1998) involved 22 subjects who had undergone cholecystectomy and had manometrically confirmed type III sphincter of Oddi (SOD) dysfunction. All subjects received an endoscopic injection of 100 mouse units of botulinum toxin into the papilla of Vater. With the exception of 1 subject with mild pancreatitis (4.5%), no side effects were observed. Six weeks after botulinum toxin A injection, 12 SOD subjects (55%) were symptom-free, and 10 subjects (45%) were not. Recurrent symptoms appeared in 11 of the 12 responders after a median period of 6 months and manometry revealed sphincter hypertension in all 11 cases; all subjects became free of complaints again after endoscopic sphincterotomy during a median follow-up of a further 15 months.

The second study (2000) involved 15 subjects with pancreatic sphincter of Oddi dysfunction with frequent attacks of acute pancreatitis within 6 months, and manometrically proven pancreatic sphincter of Oddi dysfunction. All underwent endoscopic injection of 100 units of botulinum toxin into the major papilla. Within 3 months after treatment, 12 out of 15 subjects remained asymptomatic (80% primary response). Only 1 out of 3 subjects without symptomatic benefit showed continued elevated pancreatic sphincter pressure at manometry and only this subject benefited from pancreatic sphincterotomy later on. Eleven of the 12 subjects initially responding to botulinum toxin injection developed a symptomatic relapse 6 ± 2 months after botulinum toxin treatment. These subjects then achieved long-term clinical remission from pancreatic or combined (biliary and pancreatic, n=5) sphincterotomy (median follow-up, 15 months).

Further evidence is required for a full evaluation of the efficacy of botulinum toxin therapy for sphincter of Oddi dysfunction.

Tinnitus

It has been postulated that the blockage of autonomic pathways with botulinum toxin might have a favorable impact on the perception of tinnitus. In a randomized, double-blind study, Stidham and colleagues (2005) explored the use of botulinum toxin A injections for the treatment of tinnitus in 30 subjects with unilateral or bilateral non-pulsatile tinnitus with no evidence of middle ear disease, for greater than 2 months. The subjects ranged in age from 31 to 73 years, with duration of symptoms from 5 months to 30 years, with a median duration of 72 months. Subjects were recruited from an existing population under care at a single treatment center for a variety of conditions including primary tinnitus, hearing loss, and Ménierè's disease. Subjects were randomized to receive 3 subcutaneous injections of botulinum toxin A near

the ear followed by placebo injections 4 months later; a second group received placebo injections first followed by botulinum toxin A 4 months later. Included in the data analysis were 26 subjects who completed both injections.

After treatment, subjects' responses to treatment were recorded at 1 month and again at 4 months. Following treatment with botulinum toxin A, subjective tinnitus improved in 7 subjects, worsened in 3, and 16 were unchanged. Following placebo, 2 subjects were improved, 7 worsened, and 17 were unchanged. Comparison of subjective responses in the treatment and placebo groups was statistically significant ($p<0.005$). However, using the standardized Tinnitus Handicap Inventory (THI) scale to judge response to treatment, there was no difference at 1 month between active and placebo treatments. A THI marginal statistical difference was reached only in the comparison of pre-botulinum toxin A to 4 months post-treatment ($p=0.042$). However, no other significant differences were noted when comparing the two treatments at 1 and 4 months after injections. This study is limited by its small numbers, lack of intent-to-treat analysis, as well as differing etiologies and lengths of tinnitus. The authors concluded a larger study is needed before drawing conclusions regarding the potential benefit of botulinum toxin A in the treatment of tinnitus.

Tremor

Tremor may be defined as alternate or synchronous contractions of antagonistic muscles. Some subjects 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 subjects with tremors unrelated to dystonias. One randomized study by Pahwa (1995) reported on 10 subjects with essential head tremor. Subjects were randomized to receive either botulinum injections into the sternocleidomastoid (SCM) or splenius capitus (SC) muscle. Five subjects improved in the SCM group compared to 3 in the SC group. The lack of statistical significance may be related to the small size of the study. Two randomized, placebo-controlled studies addressed essential hand tremors, enrolling 133 and 25 subjects, respectively (Brin, 2001; Jankovic, 1996). In both studies, significant advantages for botulinum toxin found on tremor symptom scales were inconsistent, and none were shown on functional outcomes. Thus, the clinical significance of these findings is unclear.

Urologic Applications

Neurogenic Detrusor Overactivity (also referred to as neurogenic overactive bladder)

Individuals with spinal cord injuries or multiple sclerosis often have incontinence-related neurogenic detrusor overactivity due to a lack of coordination between the detrusor muscles of the bladder and the external urethral sphincter muscles. Conservative therapy includes behavioral therapy and treatment with anticholinergic drugs. Many individuals are refractory to or intolerant of anticholinergic therapy. BTA has been investigated as an alternative in these individuals. Two double-blind, placebo-controlled multi-center clinical studies were conducted in subjects with urinary incontinence due to detrusor overactivity (Chancellor, 2013; Cruz 2011). A total of 691 subjects were enrolled and randomized to receive intradetrusor injections of either 200 or 300 Units of Botox (n=227, n=223, respectively) or placebo (n=241). Participant selection criteria included at least 14 weekly episodes of incontinence inadequately managed by anticholinergic drugs. In both studies, significant improvements were noted compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence. Quality of life measures also improved significantly. In 2013, Kennelly and colleagues published a planned interim analysis of the outcomes of repeat BTA in 387 of the 450 subjects originally randomized to one of the treatment arms. Subjects received up to five treatments over a course of 3 years. A sustained and consistent reduction occurred in weekly incontinence episodes across the five treatment cycles. The authors did not report any new significant adverse events outside of the known profile for BTA; urinary tract infections and urinary retention were the most commonly reported complications. The authors conclude from these findings that BTA treatment for neurogenic detrusor overactivity provided sustained and safe reductions in the incidence of incontinence and increased void volumes.

Idiopathic Overactive Bladder

Idiopathic overactive bladder is a common clinical condition describing urinary urgency with or without urgency incontinence, usually accompanied by urinary frequency. Conservative treatment includes behavioral therapy and anticholinergic drugs. BTA has also been investigated for this indication in subjects who are refractory to or intolerant of anticholinergic therapy. Chapple (2013) reported on a randomized double-blind study comparing a single intradetrusor injection of saline placebo (n=271) or 100 U of BTA in 548 participants, all of whom had an inadequate response to anticholinergic therapy and experienced more than three incontinent episodes over 3 days and more than eight micturitions per day. The primary outcome was assessed at week 12 following the treatment and consisted of the change from baseline in the number of incontinent episodes. BTA significantly decreased the number of urinary incontinence episodes per day (-2.95 episodes for the BTA group vs. -1.03 for the placebo; $p<0.001$). Additionally, reductions were seen in all baseline overactive bladder symptoms, including episodes of urinary urgency incontinence, micturition, urgency, and nocturia. Scores on the Incontinence Quality of Life (I-QOL) and Kings' Health Questionnaire (KHQ) tools were also significantly improved following BTA treatment compared with placebo ($p<0.01$). Adverse events were mainly localized to the urinary tract. However, the mean post-void residual urine volume was higher in the BTA group (46.9 ml vs. 10.1 ml at week 2; $p<0.001$), and 6.9% of BTA subjects versus 0.7% of placebo subjects initiated clean intermittent catheterization. The authors concluded that BTA 100 U was well tolerated and demonstrated significant and clinically relevant improvements in all overactive bladder (OAB) symptoms in subjects inadequately managed by anticholinergics. Nitti and colleagues (2013) reported the results of a study of 557 subjects with idiopathic overactive bladder randomized in a 1:1 fashion to receive intradetrusor injections of BTA or placebo. The selection criteria and outcomes were similar to the Chapple trial. Similarly, BTA significantly decreased the daily frequency of urinary incontinence episodes versus placebo (-2.65 vs. -0.87, $p<0.001$) and 22.9% versus 6.5% of subjects became completely continent. A larger proportion of those in the treatment group reported a positive response on the treatment benefit scale (60.8% vs. 29.2%, $p<0.001$). All other overactive bladder symptoms improved versus placebo ($p\leq0.05$). Uncomplicated urinary tract infection was the most common adverse event. A 5.4% rate of urinary retention was observed.

In 2016, Nitti reported a continuation study involving the subjects from the 2013 Chapple and 2015 Nitti study described above. This 3-year extension study provided continued treatment with onabotulinumtoxinA 100 U as needed to control overactive bladder symptoms in 839 subjects, 430 (51.3%) of whom completed the 3-year study period. The authors reported consistent mean reductions in urinary incontinence following continued treatment, ranging from -3.1 to -3.8 episodes in the overall population and -2.9 to -4.5 episodes in the discrete subgroups stratified number of treatment.

The median duration of effect was 7.6 months. The most common adverse event was urinary tract infection. The rate of de novo catheterization after the first treatment was 4.0% and it ranged from 0.6% to 1.7% after subsequent treatments.

A large RCT involving 364 women with refractory urgency urinary incontinence was reported by Amundsen in 2016. Subjects were randomly assigned to treatment with cystoscopic intradetrusor injection of 200 U of onabotulinumtoxinA (n=190) or sacral neuromodulation (n=174) and followed for 6 months. The authors reported that the onabotulinumtoxinA group had a greater reduction in 6-month mean number of episodes of urgency incontinence per day vs the neuromodulation group (−3.9 vs −3.3 episodes per day; p=0.01). No significant differences between groups were reported with regard to adverse effects (88.4 vs 85.1; p=0.22). Urinary tract infections were more frequent in the onabotulinumtoxinA group (35% vs 11%; p<0.001). The need for self-catheterization was 8% and 2% at 1 and 6 months in the onabotulinumtoxinA group. Neuromodulation device revisions and removals occurred in 3% of subjects. The authors observed that, "OnabotulinumtoxinA increased the risk of urinary tract infections and need for self-catheterizations. Overall, these findings make it uncertain whether onabotulinumtoxinA provides a clinically important net benefit compared with sacral neuromodulation." They concluded that the small daily improvement in episodes of incontinence is of uncertain clinical benefit, despite the statistical significance.

Other Urologic Indications

In a study performed by De Seze and colleagues (2002), 13 subjects with chronic urinary retention due to detrusor sphincter dyssynergia from spinal cord injury were randomized to receive perineal botulinum toxin or lidocaine injections into the external urethral sphincter. In the botulinum group, there was a significant decrease in the post-void residual volume (one of the endpoints) compared to no change in the control group receiving a lidocaine injection. Improvements were also seen in the satisfaction scores and other urodynamic outcomes.

Chen and Kuo (2004) showed positive results with botulinum toxin when comparing Botox and no treatment in subjects with urinary problems due to intracranial lesions or cerebrovascular accidents. Subjects who received a urethral injection of Botox showed improved voiding pressure and increased maximum urine flow rates (+3.1 mL/sec) compared to baseline (p<0.05). No adverse effects or withdrawals were reported.

Vaginismus

At this time, there are only three peer-reviewed published studies that address the efficacy or safety of botulinum toxin therapy for the treatment of vaginismus (Ghazizadeh, 2004; Pacik, 2015; Shafik, 2000). These studies have small numbers of participants and short-term follow-up. Until the time when such data is available, the use of this therapy is not considered the standard of care for this condition.

Whiplash-related disorder

Botulinum toxin therapy has been proposed as a treatment for whiplash-related disorders. There are only three small controlled trials for this treatment available in the peer-reviewed published literature.

Freund and colleagues (2000) conducted a randomized, double-blind, placebo-controlled study with 26 subjects with chronic neck pain (WAD-II chronic). One-half of the subjects (n=14) received 100 units botulinum toxin A diluted in 1 ml saline, while the other half received a total of 1 ml of saline alone (n=12). Five trigger points were targeted and received 0.2 ml each of injectant via a 30 gauge needle. At 4 weeks post-injection, the treatment group was significantly improved from pre-injection levels (p<0.01). The placebo group showed no statistically significant changes at any post-treatment time. The authors stated that botulinum toxin treatment of subjects with chronic WAD II neck pain resulted in a significant (p<0.01) improvement in range of motion (ROM)

A randomized, placebo-controlled clinical trial to prove efficacy of botulinum toxin for neck pain in chronic whiplash syndrome was reported by Padberg et al. (2007). Forty subjects with chronic whiplash syndrome (whiplash associated disorders grade 1 and 2) were randomly assigned to receive botulinum toxin (maximum 100 units) or placebo (saline) in muscles with increased tenderness. After 12 weeks, there was no significant difference between the two treatment groups in decrease of neck pain intensity, mean number of neck pain days, neck pain hours per day, days on which symptomatic treatment was taken, number of analgesics taken per day, and total cervical range of motion. There was also no significant difference in subjects' assessment of improvement after weeks 4, 8, and 12. The authors concluded that botulinum toxin was not proven effective in treatment of neck pain in chronic whiplash syndrome.

The most recent published article by Braker and others (2008) enrolled 20 subjects with cervical pain due to whiplash injury in a randomized controlled trial. All participants were randomly assigned to receive either 200 U of botulinum toxin A or placebo at 4 trigger points and were seen for follow-up 3, 6, 9, 12, and 24 weeks after the injections. The authors reported a time-dependent improvement in all the parameters in both groups, which was consistently larger in the botulinum toxin A-treated group, but mostly not at a significant level. Significant differences between the groups were found only in the percentages of subjects who achieved 50% or more reduction in intensity at 24 weeks (50% vs. 0%, p>0.05 and 70% vs. 11%, p>0.05, respectively). Systemic adverse effects tended to be more common in the botulinum toxin A-treated group (40% vs. 0%, p=0.07).

Wrinkles

The use of botulinum toxin for the treatment of facial or other wrinkles does not provide any proven medical benefit. Any improvement in physical appearance is considered cosmetic regarding facial and other wrinkles.

Zygomatic fractures

At this time, there are no peer-reviewed published studies that demonstrate the efficacy or safety of botulinum toxin therapy for the treatment of zygomatic fractures. Until the time when such data is available, the use of this therapy is not considered the standard of care for this condition.

Trial of alternate botulinum toxin products

At this time, there is no available evidence in the peer-reviewed published literature addressing the use of alternate botulinum toxin products in the instance of treatment failure with a first botulinum toxin product. Until such data is available, such treatment is not supported by sufficient evidence.

Background/Overview

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 this country, four preparations of botulinum are available, produced by two different strains of bacteria: type A (Botox [onabotulinumtoxinA], Dysport [abobotulinumtoxinA], and Xeomin [incobotulinumtoxinA]) and type B (Myobloc [rimabotulinumtoxinB]). When administered intramuscularly, all botulinum toxins reduce muscle tone by interfering with the release of acetylcholine from nerve endings. However, it should be noted that these drugs are not interchangeable and the potency ratios for dosing cannot be converted. Careful adherence to the specific instructions for dosing in the package insert is recommended.

The U.S. Food and Drug Administration (FDA) approved label for Botox states that it is indicated for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain, primary axillary hyperhidrosis that is inadequately managed with topical agents, and strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or facial nerve (VII nerve) disorders in individuals older than 12 years, urinary incontinence due to detrusor overactivity associated a neurologic condition, prophylaxis of chronic migraine headaches in adults, upper limb spasticity in adults, lower limb spasticity, and for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults less than or equal to 65 years of age.

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

The FDA approved label for Dysport specifies that it is indicated for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain, upper limb spasticity in adults, lower limb spasticity in pediatric patients 2 years of age and older, and the temporary improvement in the appearance of moderate to severe glabellar lines in adults younger than 65 years of age.

Xeomin has received FDA approval for the treatment of cervical dystonia in adults to reduce the severity of abnormal head position and neck pain, abnormal spasm of the eyelids blepharospasm in adults, adults with upper limb spasticity, and the temporary improvement in the appearance of moderate to severe frown lines between the eyebrows (glabellar lines) in adults.

Dystonia is a general term describing a state of abnormal or disordered tonicity of muscle. As an example, achalasia is a dystonia of the lower esophageal sphincter, while cervical dystonia is also known as torticollis. Spasticity is a subset of dystonia, describing a velocity-dependent increase in tonic-stretch reflexes with exaggerated tendon jerks. Spasticity typically is associated with injuries to the central nervous system. Spasticity is a common feature of cerebral palsy. Since its FDA approval in 1991, Botox has been used for a wide variety of off-label indications; all associated with dystonia, ranging from achalasia, spasticity after strokes, cerebral palsy, and anal fissures. In addition to widening indications, Botox has also been used in children under 12, particularly for the treatment of cerebral palsy.

The use of botulinum toxin for the treatment of cervical dystonia and spasmodic torticollis may be assessed using specific rating scales such as the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scale, which can aid in judging the individual's response to treatment.

It must be noted that there are several FDA approved warnings in the package inserts for Botox, Dysport, Myobloc, and Xeomin regarding potential complications. The first warning addressed potential problems when these drugs are used by individuals with peripheral motor neuropathic diseases (for example, amyotrophic lateral sclerosis [ALS], or motor neuropathy) or neuromuscular junctional disorders (for example, myasthenia gravis or Lambert-Eaton syndrome); "Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of either of these drugs." The second warning addresses potential complications related to spread from the initial injection site. The following was released by the FDA to health care professionals:

- Be aware that a *Boxed Warning* has been added to the prescribing information to highlight that botulinum toxin may spread from the area of injection to produce symptoms consistent with botulism. Symptoms such as unexpected loss of strength or muscle weakness, hoarseness or trouble talking (dysphonia), trouble saying words clearly (dysarthria), loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids may occur.
- Understand that swallowing and breathing difficulties can be life-threatening and there have been reports of deaths related to the effects of spread of botulinum toxin.
- Be aware that children treated for spasticity are at greatest risk for these symptoms, but symptoms can also occur in adults treated for spasticity and other conditions.
- Be aware that cases of toxin spread have occurred at botulinum toxin doses comparable to those used to treat cervical dystonia and at lower doses.
- Be aware that no definitive serious adverse event reports of distant spread of toxin effect have been associated with dermatologic use of Botox/Botox Cosmetic at approved doses.
- Be aware that no definitive serious adverse event reports of distant spread of toxin effect have been associated with Botox for blepharospasm or for strabismus at approved doses.

In August 2015 the FDA added the following warning to the label for Botox regarding serious adverse reactions with unapproved use:

> Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

Finally, the FDA added this warning to the label of Botox in January 2016 regarding bronchitis and upper respiratory tract infections in patients treated for spasticity:

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with Botox (3% at 251 Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with Botox (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with Botox (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

Definitions

Achalasia: A condition involving the esophagus and the muscle that separates the esophagus from the stomach. In this condition, the esophagus is less able to move food toward the stomach and the valve from the esophagus to the stomach does not relax adequately during swallowing to allow the passage of food.

Benign prostatic hyperplasia: A condition characterized by non-cancerous overgrowth of the prostate gland leading to urinary dysfunction and other problems.

Blepharospasm: A condition characterized by abnormal, involuntary blinking or spasm of the eyelids.

Botulinum toxin: A powerful drug that can be used to paralyze the nerves that motivate muscle movement.

Cervical dystonia: A nervous system-related movement disorder characterized by neck muscles contracting involuntarily, causing abnormal movements and postures of the head and neck.

Dystonia: A nervous system related movement disorder characterized by sustained muscle contractions.

Epicondylitis: A condition due to inflammation of the epicondyle (a part of the end of the humerus bone) or of the tissues adjoining the epicondyle of the humerus; also known as tennis elbow.

Facial nerve VII disorders (also known as hemifacial spasm): A condition where the face muscles on one side of an individual's face contract involuntarily.

Hereditary spastic paraparesis (also known as familial spastic paralysis or parapalegia): A group of genetic disorders that are characterized by progressive weakness and spasticity (stiffness) of the legs. Symptoms may occur alone or in combination with a number of other neurological symptoms.

Hirschsprung disease: A congenital condition that causes poor muscle movement in the bowel. It is frequently associated with blockage of the large intestine.

Idiopathic overactive bladder: A common clinical condition describing urinary urgency with or without urgency incontinence, usually accompanied by urinary.

Idiopathic torsion dystonia (also known as primary dystonia): A group of genetic diseases of the nervous system, which cause involuntary abnormal twisting movements of the body.

Infantile cerebral palsy: A group of disorders characterized by loss of movement or loss of other nerve functions; these disorders are caused by injuries to the brain that occur during fetal development or near the time of birth.

Migraine day: One calendar day consisting of 4 hours or more of continuous migraine headache.

Multiple sclerosis: A disorder of the brain and spinal cord caused by progressive damage to the outer covering of nerve cells. This results in decreased nerve function leading to a variety of symptoms including muscle spasticity, atrophy, weakness, paralysis, or tremor of the limbs.

Neurogenic overactive bladder (also referred to as detrusor overactivity or detrusor sphincter dyssynergia): A disturbance of the normal relationship between bladder (detrusor) contraction and sphincter relaxation during voluntary or involuntary voiding efforts due to a lack of coordination between the detrusor muscles of the bladder and the external urethral sphincter muscles.

Neuromyelitis optica (also known as Devic's disease): A rare nerve disorder characterized by inflammation and swelling of the nerves in the eyes and spinal cord. Affected individuals may also experience loss of visual clarity (acuity), mild paralysis, and loss of bladder and bowel control.

Nystagmus: A condition characterized by an involuntary, rapid, rhythmic movement of the eyeball, which may be horizontal, vertical, rotary or mixed.

Organic writer's cramp: A task-specific focal dystonia of the hand; symptoms usually appear when a person is trying to do a task that requires fine motor movements; symptoms may appear only during a particular type of movement, such as writing or playing the piano, but the dystonia may spread to affect many tasks.

Orofacial dyskinesia (also known as jaw closure dystonia)**:** A condition where an individual's face or mouth is subject to involuntary movements due to muscle contractions.

Schilder's Disease: A rare progressive disease affecting the brain and nerves; symptoms may include dementia, difficulty speaking, seizures, personality changes, poor attention, and tremors.

Spasmodic dysphonia or laryngeal dystonia: A disorder of speech due to abnormal control of the laryngeal muscles present only during the specific task of speaking.

Spasmodic torticollis: A congenital condition that is caused by a chronically contracted muscle on one side of the head that pulls the head (ear) down toward one shoulder as the chin tilts to the opposite side.

Spastic hemiplegia: A condition where one half of an individual's body is subject to involuntary muscle contractions leading to paralysis.

Sphincter of Oddi: A muscular structure that controls the flow of secretions from the liver, pancreas, and gallbladder into the duodenum of the small intestine; also known as the hepatopancreatic sphincter or Glisson's sphincter.

Strabismus: A condition where an individual's eyes are misaligned and point in different directions due to involuntary contractions of the muscles controlling the eyes.

Symptomatic torsion dystonia: A group of genetic diseases of the nervous system that cause involuntary abnormal twisting movements of the body.

Tinnitus: A perception of sound in the head when no outside sound is present. It typically referred to as "ringing in the ears" or "head noise," but other forms of sound have been described such as hissing, roaring, pulsing, whooshing, chirping, whistling and clicking.

Vaginismus: A condition characterized by painful spasmodic contraction of the vagina.

Whiplash injury: A musculoskeletal injury due to hyperextension-hyperflexion of the neck.

Zygomatic fractures: A fracture of the zygoma, the portion of the skull that forms part of the floor and lateral wall of the orbit of the eye.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Medically Necessary:

CPT

31573	Laryngoscopy, flexible; with therapeutic injection(s) (eg, chemodenervation agent or corticosteroid, injected percutaneous, transoral, or via endoscope channel), unilateral
46505	Chemodenervation of internal anal sphincter [for diagnosis of anal fissure]
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder [for specified related bladder and incontinence disorders]
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous, (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64642	Chemodenervation of one extremity; 1-4 muscle(s)
64643	Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s)
64644	Chemodenervation of one extremity; 5 or more muscles
64645	Chemodenervation of one extremity; each additional extremity, 5 or more muscles
64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)
64647	Chemodenervation of trunk muscle(s); 6 or more muscles
67345	Chemodenervation of extraocular muscle [for diagnosis of strabismus]

HCPCS

J0585	Injection, onabotulinumtoxinA, 1 unit [e.g., Botox]
J0586	Injection, abobotulinumtoxinA, 5 units [Dysport]
J0587	Injection, rimabotulinumtoxinB, 100 units [Myobloc]
J0588	Injection, incobotulinumtoxinA, 1 unit [Xeomin]
S2340	Chemodenervation of abductor muscle(s) of vocal cord
S2341	Chemodenervation of adductor muscle(s) of vocal cord

ICD-10 Diagnosis

G11.4	Hereditary spastic paraplegia
G24.01-G24.09	Drug induced dystonia
G24.1-G24.2	Genetic torsion dystonia, idiopathic nonfamilial dystonia
G24.4	Idiopathic orofacial dystonia
G24.5	Blepharospasm
G24.8	Other dystonia
G35	Multiple sclerosis
G36.0	Neuromyelitis optica
G37.0	Diffuse sclerosis of central nervous system (Schilder's disease)
G37.5	Concentric sclerosis [Balo] of central nervous system
G51.0-G51.9	Facial nerve disorders
G80.0-G80.9	Cerebral palsy
G81.10-G81.14	Spastic hemiplegia
H49.00-H49.9	Paralytic strabismus

H50.00-H50.9	Other strabismus
J38.3	Other diseases of vocal cords (spastic dysphonia)
J38.5	Laryngeal spasm
K22.0	Achalasia of cardia (cardiospasm)
K60.0-K60.2	Anal fissure
R49.8-R49.9	Other and unspecified voice and resonance disorders

When services may be Medically Necessary when criteria are met:

CPT

46505	Chemodenervation of internal anal sphincter [for diagnosis of Hirschsprung's disease]
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder [for specified bladder and incontinence disorders]
64611	Chemodenervation of parotid and submandibular salivary glands, bilateral [for significant drooling]
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm or hemifacial spasm)
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous, (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64642	Chemodenervation of one extremity; 1-4 muscle(s)
64643	Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s)
64644	Chemodenervation of one extremity; 5 or more muscles
64645	Chemodenervation of one extremity; each additional extremity, 5 or more muscles
64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)
64647	Chemodenervation of trunk muscle(s); 6 or more muscles
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (eg, scalp, face, neck), per day

HCPCS

J0585	Injection, onabotulinumtoxinA, 1 unit [Botox]
J0586	Injection, abobotulinumtoxinA, 5 units [Dysport]
J0587	Injection, rimabotulinumtoxinB, 100 units [Myobloc]
J0588	Injection, incobotulinumtoxinA, 1 unit [Xeomin]
S2340	Chemodenervation of abductor muscle(s) of vocal cord
S2341	Chemodenervation of adductor muscle(s) of vocal cord

ICD-10 Diagnosis

G24.3	Spasmodic torticollis
G24.9	Dystonia, unspecified
G25.89	Other specified extrapyramidal and movement disorders [specified as organic writer's cramp]
G43.001-G43.919	Migraine
G83.4	Cauda equina syndrome
G95.89	Other specified diseases of spinal cord (cord bladder NOS)
I69.00-I69.998	Sequelae of cerebrovascular disease
K11.7	Disturbance of salivary secretion
L74.510-L74.519	Primary focal hyperhidrosis
L74.52	Secondary focal hyperhidrosis
M43.6	Torticollis
N31.0-N31.9	Neuromuscular dysfunction of bladder, not elsewhere classified
N32.81	Overactive bladder (detrusor muscle hyperactivity)
N36.44	Muscular disorders of urethra (bladder sphincter dyssynergy)
N39.3	Stress incontinence
N39.41-N39.498	Other specified urinary incontinence
Q43.1	Hirschsprung's disease
Q68.0	Congenital deformity of sternocleidomastoid muscle
R13.10-R13.19	Dysphagia
R32	Unspecified urinary incontinence
R61	Generalized hyperhidrosis
S06.0X0S-S06.9X9S	Intracranial injury, sequela [code range, includes codes within this range with 7th character 'S']
S14.101S-S14.159S	Other and unspecified injury of cervical spinal cord [code range, includes codes within this range with 7th character 'S']
S24.101S-S24.159S	Other and unspecified injury of thoracic spinal cord [code range, includes codes within this range with 7th character 'S']
S34.101S-S34.139S	Other and unspecified injury of lumbar and sacral spinal cord [code range, includes codes within this range with 7th character 'S']

When services are Not Medically Necessary:
For the codes listed above for those indications listed in the Position Statement section as not medically necessary when criteria are not met.

When services are Cosmetic and Not Medically Necessary:
For the procedure and botulinum toxin codes listed above for the following diagnoses, or when the code describes a procedure indicated in the Position Statement section as cosmetic and not medically necessary.

ICD-10 Diagnosis	
L57.4	Cutis laxa senilis
L91.8-L91.9	Other and unspecified hypertrophic disorders of the skin
Z41.1	Encounter for cosmetic surgery

When services are Investigational and Not Medically Necessary:
For the codes listed above when criteria are not met or for all other diagnoses not listed, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Revised	08/03/2017	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated CECEA section with new indication for Dysport. Updated Rationale and References sections.
Revised	05/04/2017	MPTAC review. Moved treatment of hyperhidrosis with botulinum toxin from MED.00032. Updated Description/Scope, Rationale, Coding and References sections.
Revised	02/02/2017	MPTAC review. Changed title of the "Preferred Agents" section to "Clinically Equivalent Cost Effective Agents."
Reviewed	11/03/2016	MPTAC review. Updated formatting in Position Statement section. Added new section addressing preferred agents. Updated Rationale and Reference sections. Updated Coding section with 01/01/2017 CPT changes.
Revised	05/05/2016	MPTAC review. Minor clarification to MN criteria for cervical dystonia. Updated Background and Reference sections.
Revised	11/05/2015	MPTAC review. Made minor format change in Position Statement. Revised Rationale section to update International Headache Society headache classification information. Updated Reference section and removed ICD-9 codes from Coding section.
Revised	08/06/2015	MPTAC review. Replaced "migraine" days with "headache" days in medically necessary criteria for treatment of migraine headaches. Added brachial plexus palsy as investigational and not medically necessary. Updated Rationale and References sections.
Revised	05/07/2015	MPTAC review. Clarified criteria for continuation of therapy for migraine headaches. Added the treatment of functional obstruction caused by the inability of the internal anal sphincter to relax in individuals with Hirschsprung disease who have undergone prior surgical treatment as medically necessary. Clarified investigational and not medically necessary statement addressing Hirschsprung disease. Updated Rationale, Coding and References sections.
Revised	05/15/2014	MPTAC review. Added "for individuals who met criteria for an initial trial" to Medically Necessary statement regarding continuation of treatment. Added new criteria to medically necessary position statement to distinguish neurogenic overactive bladder from idiopathic overactive bladder. Added several indications to Investigational and Not Medically Necessary section. Updated Rationale, Coding and Reference sections.
	01/01/2014	Updated Coding section with 01/01/2014 CPT changes; removed 64613, 64614 deleted 12/31/2013.
Revised	05/09/2013	MPTAC review. Added new position statement regarding repeat treatment with second botulinum toxin product after previous treatment failure with a first botulinum toxin product. Updated Rationale and Reference sections.
	01/01/2013	Updated Coding section with 01/01/2013 CPT changes.
Reviewed	05/10/2012	MPTAC review. Updated Coding and Reference sections.
	01/01/2012	Updated Coding section with 01/01/2012 HCPCS changes; removed Q2040 deleted 12/31/2011.
Revised	05/19/2011	MPTAC review. Added treatment of hemifacial spasm to medically necessary section. Updated Reference section.
	04/01/2011	Updated Coding section with 04/01/2011 HCPCS changes; removed C9278 deleted 03/31/2011.
	01/01/2011	Updated Coding section with 01/01/2011 CPT and HCPCS changes.

Revised	11/18/2010	MPTAC review. Added treatment of tinnitus to investigational and not medically necessary section from MED.00073 Treatment of Tinnitus, which was archived. The MPTAC voted to add treatment of chronic migraine headache as medically necessary with criteria and investigational and not medically necessary when criteria are not met with final criteria developed after the meeting and circulated to MPTAC for review and approval by email vote which concluded on 12/1/2010 with approval of the criteria. Clarified that treatment of episodic migraine headaches is investigational and not medically necessary. Updated Rationale, Definitions, Background, and Reference sections.
Revised	08/19/2010	MPTAC review. Revised medically necessary statement for spasticity related to stroke and spinal cord injury to add traumatic brain injury. Added Xeomin (IncobotulinumtoxinA) to document. Updated Rationale, Coding and Reference sections.
	01/01/2010	Updated Coding section to include 01/01/2010 HCPCS changes.
Revised	08/27/2009	MPTAC review. Removed "Equinas foot" from medically necessary section. Updated Background, Definitions, Coding, Reference and Index sections.
Revised	08/28/2008	MPTAC review. Added the following to the investigational and not medically necessary section: benign prostatic hypertrophy, disorders of the esophagus, epicondylitis, nystagmus, sphincter of Oddi dysfunction, vaginismus, whiplash-associated disorders and zygomatic fractures. Updated Rationale, Definitions and Reference sections.
Revised	11/29/2007	MPTAC review. Added new criteria for the medically necessary use of botulinum toxin for the treatment of cervical dystonia (spasmodic torticollis). Added not medically necessary statement for cervical dystonia (spasmodic torticollis) when criteria are not met. The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary" and the phrase "cosmetic/not medically necessary" was clarified to read "cosmetic and not medically necessary." Updated Coding and Background sections.
Reviewed	05/17/2007	MPTAC review. Deleted tinnitus from document and added note to see MED.00073 Treatment of Tinnitus. Updated Reference section.
Reviewed	12/07/2006	MPTAC review. Rationale updated to support botulinum toxin use in headache remains not medically necessary. No change to position statement. References updated.
Revised	09/14/2006	MPTAC revision. Document updated to address urologic indications; position statement revised to indicate treatment of incontinence related to detrusor overactivity due to spinal cord injury is medically necessary. Treatment of tinnitus is identified as investigational. References updated.
Revised	03/23/2006	MPTAC revision. Clarified background to include all FDA approved indications. Reference made to MED.00032.
Revised	12/01/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organization	Last Review Date	Document Number	Title
Anthem, Inc.	10/27/2004	DRUG.00006	Botulinum Toxin
WellPoint Health Networks, Inc.	09/23/2004	8.01.03	Botulinum Toxin Injections

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