INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE
This policy refers to the following drug products:

Botulinum toxin type A
- abobotulinumtoxinA (Dysport™)
- incobotulinumtoxinA (Xeomin®)
- onabotulinumtoxinA (Botox®)

Botulinum toxin type B
- rimabotulinumtoxinB (Myobloc®)

The following information pertains to medical necessity review:

A. General Requirements (applicable to all medical necessity requests):
   1) For initial therapy, both of the following:

   Botulinum Toxins A and B: Drug Policy (Effective 09/01/2014)

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a. Diagnosis
   AND
b. Medical records documenting both of the following:
   1. History and physical examination documenting the severity of the condition
      AND
   2. Laboratory results or diagnostic evidence supporting the indication for which
      botulinum toxin is requested

2) For continuation of therapy, both of the following:
   a. Documentation of positive clinical response to botulinum toxin therapy
   AND
   b. Statement of expected frequency and duration of proposed botulinum toxin treatment

3) Frequency of botulinum toxin administration, regardless of diagnosis, does not exceed
   every 12 weeks

B. Diagnosis-Specific Requirements
The information below indicates additional requirements for those indications having specific
medical necessity criteria in the list of proven indications.

AbobotulinumtoxinA (Dysport, botulinum toxin type A) is proven in the treatment of the
following conditions:

1) Achalasia

   Additional information to support medical necessity review where applicable:
   AbobotulinumtoxinA is medically necessary for the treatment of achalasia when both of the
   following criteria are met:
   A. Diagnosis of achalasia
   AND
   B. History of failure, contraindication, or intolerance to one of the following: Refer to
      Benefit Considerations for specific state guidance.
      1. Long-acting nitrate
      2. Calcium channel blocker

2) Anal fissures, chronic

   Additional information to support medical necessity review where applicable:
   AbobotulinumtoxinA is medically necessary for the treatment of chronic anal fissures when
   all of the following criteria are met:
   A. Diagnosis of chronic anal fissure
   AND
   B. At least 2 months of symptoms including one of the following: Refer to
      Benefit Considerations for specific state guidance.
      1. Nocturnal pain and bleeding
      2. Postdefecation pain
   AND
   C. History of failure, contraindication, or intolerance to two of the following conventional
      therapies: Refer to Benefit Considerations for specific state guidance.
      1. Topical nitrate
      2. Oral calcium channel blocker (e.g., diltiazem, nifedipine)
      3. Topical calcium channel blocker (e.g., diltiazem, nifedipine)

3) Cervical dystonia (also known as spasmodic torticollis)

   Additional information to support medical necessity review where applicable:
   AbobotulinumtoxinA is medically necessary for the treatment of cervical dystonia when
   both of the following criteria are met:
A. Diagnosis of cervical dystonia
   AND
B. Symptoms including both of the following:
   1. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
   2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

4) Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease

Additional information to support medical necessity review where applicable:
AbobotulinumtoxinA is medically necessary when both of the following criteria are met:
A. One of the following:
   1. Diagnosis of detrusor overactivity
   2. Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease
   AND
B. History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine) Refer to Benefit Considerations for specific state guidance.

5) Hand dystonia (writer's, musician's or typist's cramp)
6) Hand tremor
7) Hemifacial spasm (seventh cranial nerve disorders)
8) Hyperhidrosis including gustatory sweating (Frey's Syndrome)
9) Oromandibular dystonia
10) Piriformis syndrome
11) Sialorrhea
12) Spasmodic dysphonia (laryngeal dystonia)
13) Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or tumor of the brain or spinal cord
14) Strabismus and blepharospasm associated with dystonia
15) Tongue dystonia
16) Torsion dystonia
17) Voice tremor

IncobotulinumtoxinA (Xeomin, botulinum toxin type A) is proven in the treatment of the following conditions:
1) Blepharospasm associated with dystonia
2) Cervical dystonia (spasmodic torticollis)

Additional information to support medical necessity review where applicable:
IncobotulinumtoxinA is medically necessary for the treatment of cervical dystonia (spasmodic torticollis) when both of the following criteria are met:
A. Diagnosis of cervical dystonia
   AND
B. Symptoms including both of the following:
   1. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
   2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

3) Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or
OnabotulinumtoxinA (Botox, botulinum toxin type A), is proven in the treatment of the following conditions:

1) Achalasia

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is medically necessary for the treatment of achalasia when both of the following criteria are met:
A. Diagnosis of achalasia
AND
B. History of failure, contraindication, or intolerance to one of the following: Refer to Benefit Considerations for specific state guidance.
   1. Long-acting nitrate
   2. Calcium channel blocker

2) Anal fissures, chronic

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is medically necessary for the treatment of chronic anal fissures when both of the following criteria are met:
A. Diagnosis of chronic anal fissure
AND
B. At least 2 months of symptoms including one of the following:
   1. Nocturnal pain and bleeding
   2. Postdefecation pain
AND
C. History of failure, contraindication, or intolerance to two of the following conventional therapies: Refer to Benefit Considerations for specific state guidance.
   1. Topical nitrates
   2. Oral calcium channel blockers (e.g., diltiazem, nifedipine)
   3. Topical calcium channel blockers (e.g., diltiazem, nifedipine)

3) Cervical dystonia (also known as spasmodic torticollis)

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:
A. Diagnosis of cervical dystonia
AND
B. Symptoms including both of the following:
   1. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
   2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

4) Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is medically necessary when both of the following criteria are met:
A. One of the following:
   1. Diagnosis of detrusor overactivity
2. Diagnosis of detrusor-sphinctor dyssynergia due to spinal cord injury or disease
   AND
B. History of failure, contraindication, or intolerance to two anticholinergic medications
   (e.g., oxybutynin, trospium, darifenacin, tolterodine) Refer to Benefit Considerations
   for specific state guidance.

5) Hand dystonia (writer’s, musician’s or typist’s cramp) \(^{147,302,305}\)
6) Hand tremor \(^{12-3,43,147,166,302}\)
7) Hemifacial spasm (seventh cranial nerve disorders) \(^{84-7,104-8,147,165,302}\)
8) Hyperhidrosis \(^{1,138,302}\) including gustatory sweating (Frey’s Syndrome) \(^{45-8,76,136-8,192}\)
9) Migraine headache, chronic \(^{1,287,289,300,302}\) defined by both of the following:
   A. Greater than or equal to 15 headache days per month, of which at least 50% are
      migraine or probable migraine
   B. Headaches last 4 hours per day or longer

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is medically necessary for the prophylaxis of chronic migraine when all
of the following criteria are met:
   A. Diagnosis of chronic migraine, defined by both of the following:
      1. Greater than or equal to 15 headache days per month, of which at least 50% are
         migraine or probable migraine
      2. Headaches last 4 hours per day or longer
   AND
B. History of failure (after a trial of at least two months), contraindication, or intolerance
   to prophylactic therapy with one agent from two of the following therapeutic classes:
   Refer to Benefit Considerations for specific state guidance.
      1. Antiepileptic drug (e.g., divalproex sodium, sodium valproate, topiramate)
      2. Beta blocker (e.g., metoprolol, propranolol, timolol)
      3. Antidepressant (e.g., amitriptyline, venlafaxine)
      4. ACE inhibitor (e.g., lisinopril)
      5. Angiotensin receptor blocker (e.g., candesartan)
      6. Alpha agonist (e.g., clonidine, guanfacine)
      7. Antihistamine (e.g., cyproheptadine)
   AND
C. OnabotulinumtoxinA dose does not exceed 155 units administered intramuscularly
   divided over 31 injection sites every 12 weeks

10) Oromandibular dystonia \(^{4-7,11,126}\)
11) Overactive bladder \(^{1,302}\)

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is medically necessary for the treatment of overactive bladder when all
of the following criteria are met:
   A. Diagnosis of overactive bladder
   AND
   B. One of the following symptoms:
      1. Urge urinary incontinence
      2. Urgency
      3. Frequency
   AND
   C. History of failure, contraindication, or intolerance to two anticholinergic medications
      (e.g., oxybutynin, trospium, darifenacin, tolterodine) Refer to Benefit Considerations
      for specific state guidance.
      AND
D. OnabotulinumtoxinA dose does not exceed 100 units divided over 20 injection sites every 12 weeks

12) Piriformis syndrome
13) Sialorrhea
14) Spasmodic dysphonia (laryngeal dystonia)
15) Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or tumor of the brain or spinal cord
16) Strabismus and blepharospasm associated with dystonia
17) Tongue dystonia
18) Torsion dystonia
19) Voice tremor

RimabotulinumtoxinB (Myobloc, botulinum toxin type B) is proven in the treatment of the following conditions:
1) Cervical dystonia (also known as spasmodic torticollis)

Additional information to support medical necessity review where applicable:
RimabotulinumtoxinB is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:
A. Diagnosis of cervical dystonia
AND
B. Symptoms including both of the following:
1. Sustained head tilt or abnormal posturing with limited range of motion resulting in pain and/or functional impairment
2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

2) Detrusor overactivity (also known as detrusor hyperreflexia)

Additional information to support medical necessity review where applicable:
RimabotulinumtoxinB is medically necessary when both of the following criteria are met:
A. Diagnosis of neurogenic detrusor overactivity
AND
B. History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine) Refer to Benefit Considerations for specific state guidance.

3) Sialorrhea

AbobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and rimabotulinumtoxinB (Myobloc) are unproven and not medically necessary for the treatment of chronic migraine headache.

Botulinum toxin types A and B are unproven and not medically necessary for the treatment of the following conditions:
1) Acquired nystagmus
2) Anismus (pelvic floor dyssynergia)
3) Benign prostatic hyperplasia
4) Brachial plexus palsy
5) Chronic daily headache

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6) Chronic low back pain 60,138,302
7) Chronic prostatic pain 53,146
8) Cricopharyngeal dysphagia 42,64-5,148-64
9) Epiphora following salivary gland transplantation 77
10) Esophageal spasm 94,190-1
11) Gastroparesis (including diabetic gastroparesis) 89,90,98,145,270-7,292,302
12) Gustatory epiphora (Crocodile tears) 48,77,193-5
13) Head tremor 14-15
14) Lateral epicondylitis (tennis elbow) 95,248-51
15) Lichen simplex 94
16) Lower urinary tract (voiding) dysfunction 71,88,122-3,146
17) Motor tics 52,189
18) Myofascial pain syndrome 59,75,96,226-36,290,303
19) Nasal hypersecretion 125,265-6
20) Pain and/or wound healing after hemorrhoidectomy 146,291
21) Pancreas divisum 72
22) Pelvic floor spasticity (and associated pain conditions) 146,291
23) Postparotidectomy sialoceles 56
24) Post-thoracotomy pseudoangina 75
25) Proctalgia fugax 82,146,292
26) Severe bruxism 57,80,205-12
27) Severe paradoxical vocal cord movement 55,204
28) Sphincter of Oddi dysfunction 50,102,200-3
29) Stiff-person syndrome 37,254
30) Temporomandibular disorders 58,213-25,243
31) Tension headache 32-33,61,103,127-9,138,174-6,299
32) Thyroid associated ophthalmopathy 73,239-42
33) Tourette's syndrome 24,189,261-4
34) Traumatic sixth nerve palsy 91,256-9
35) Trigeminal neuralgia 293-295
36) Trismus and stridor in amyotrophic lateral sclerosis 78,245

Centers for Medicare and Medicaid Services (CMS):
National Coverage Determinations (NCDs) do not exist for botulinum toxins at this time. Local Coverage Determinations (LCDs) exist for the following botulinum toxin products: Botox (onabotulinumtoxinA), Myobloc (rimabotulinumtoxinB), Dysport (abobotulinumtoxinA) and Xeomin (incobotulinumtoxinA). Refer to the LCDs for Botulinum Toxins, Botulinum Toxin Type A & Type B, Botulinum Toxin Types A and B, Botulinum Toxin Types A and B Policy, Drugs and Biologicals: Botulinum Toxins and Chemodenervation.

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf. (Accessed May 16, 2014)

**BENEFIT CONSIDERATIONS**

Botulinum toxin type A and B are cosmetic when used to improve appearance, or in the absence of physiological functional impairment that would be improved by their use. Most UnitedHealthcare Certificates of Coverage (COCs) and Summary Plan Descriptions (SPDs) exclude benefit coverage for cosmetic services. In addition, most Certificates of Coverage and many Summary Plan Descriptions explicitly exclude benefit coverage for medical and surgical
treatment of excessive sweating (hyperhidrosis). The enrollee-specific benefit document must be reviewed to determine what benefits, if any, exist for treatment of hyperhidrosis.

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

**BACKGROUND**

There are seven serologically distinct forms of botulinum toxin, A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain. They all inhibit acetylcholine release at the neuromuscular junction via the enzymatic inactivation of a protein that is required for the docking and fusion process involved in the release of acetylcholine. Each neurotoxin works at a distinct site. Botulinum toxin type A cleaves the protein SNAP-25 and botulinum toxin type B cleaves synaptobrevin, both of these proteins are part of a protein complex necessary for proper docking and fusion.1,2,81,288

The potency units of botulinum toxins are specific to the preparation and assay method utilized. They are not interchangeable and, therefore, the units of biological activity cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.1,2,81,288

**CLINICAL EVIDENCE**

**Acquired nystagmus:**
The use of BTX-A for the treatment of acquired nystagmus was studied in an open-label trial involving 6 patients.18 These patients received a total of 17 injections and in each case distance visual acuity improved both subjectively and objectively. Eye movement recordings demonstrated a significant reduction in the amplitude but not the frequency of the oscillations. In another open-label trial, 12 patients with acquired nystagmus received a total of 72 injections of BTX-A.19 Objective improvements in visual acuity occurred in 8 of the 12 patients and an additional 2 patients reported subjective improvements. In an open-label trial, 3 patients with acquired nystagmus were injected with BTX-A.20 The injections either abolished or reduced the components of the nystagmus in the treated eye in each individual. Visual acuity improved in one patient, was unchanged in another and worsened in the third patient. Each patient experienced side effects from the BTX-A injection and none elected to continue with the treatment. Another report172 of two patients with acquired nystagmus were injected with 25 units of botulinum A toxin into the retrobulbar space of one eye. Visual acuity improved in one patient and both experienced improvements in ability to read and watch television, with improvements lasting 5 to 13 weeks. Two patients with acquired pendular nystagmus received botulinum in the horizontal rectus muscle of the right eye.173 The horizontal component of the nystagmus was eliminated for approximately 2 months and a small improvement of vision occurred. In one patient, the horizontal component of nystagmus increased in the non-injected eye. Neither patient elected further botulinum injections.
**Chronic low back pain:**
In a randomized, double-blind, placebo controlled trial, the efficacy of BTX-A was studied in the treatment of 31 patients with chronic low back pain. Patients received 5 injections of 40 U BTX-A or placebo at 5 lumbar or 5 lumbosacral sites on the side with pain. Efficacy measures included a Visual Analog Scale (VAS) to measure low back pain intensity and the Oswestry Low Back Pain Questionnaire (OLBPQ) which consists of 10 subsets of questions which deal with pain and activities of daily living. A significant response on the VAS was considered to be a 50% or greater reduction in pain and for the OLBPQ, at least a 2-grade improvement in one or more functional areas in addition to the pain subset. At 3 weeks, 73% of the BTX-A group had >50% pain relief compared to 25% in the placebo group (p = 0.012). At 8 weeks, 60% of the BTX-A group vs. 12.5% of the placebo group experienced >50% pain relief (p = 0.009). At 8 weeks, 66.7% of the BTX-A group and 18.8% of the placebo group showed improvements in OLBPQ (p = 0.011). While this study yielded positive results, it is important to note that the pathology of the back pain was mixed and the patient population was small. Based upon this single Class II study, the American Academy of Neurology (AAN) concluded that botulinum neurotoxin (BoNT) is possibly effective for the treatment of chronic predominantly unilateral low back pain (Level C). However, the panel stated that larger randomized-placebo controlled studies with a homogenous subject population must occur to define the role, if any, of BTX-A in the treatment of chronic low back pain.

**Head tremor:**
In a double-blind, placebo-controlled, cross-over trial, the effects of botulinum toxin type A (BTX-A) in 10 patients with essential head tremor was assessed. Patients were assessed 2, 4, and 8 weeks after the injections. There was moderate to marked objective improvement in 5 patients after BTX-A injection and in 1 after placebo. Subjective improvements occurred in 5 patients after BTX-A and 3 patients after placebo. Neither the objective nor subjective improvements were statistically significant. In an open-label trial, 43 patients with head tremor (29 with tremulous cervical dystonia and 14 without dystonia) were treated with BTX-A. Patients were assessed clinically using the Tsui scale and a 4 point pain scale. Patients were assessed quantitatively with a bidirectional accelerometer. Significant improvements were found 2 to 3 weeks post injection in the Tsui scale (p<0.001) and the pain scale (p<0.05) for both sets of patients. The amplitudes of the tremors were reduced significantly (p<0.05) although the frequency was unchanged compared to baseline values in both groups.

**Motor tics:**
In a double-blind, crossover trial, 18 patients with simple motor tics were randomized to treatment with either BTX-A or placebo. Variable doses of BTX-A were injected into the muscle that was suspected to be involved in the motor tic. The dose used was similar to doses used in the treatment of the suspected muscle in other movement disorders. The primary outcome measure was the proportional change in the number of tics per minute at week 2 vs. baseline. Secondary measures included the Shapiro Tourette Syndrome Severity Scale scores, premonitory and urge sensation scores (range 0 - 4). At 2 weeks, BTX-A treatment resulted in a 39% reduction in tics vs. a 5.8% increase with placebo (net effect 37% reduction with BTX-A, p=0.0007). BTX-A resulted in a 0.46 point reduction in urge score vs. 0.49 point increase with placebo (net effect 0.94, p=0.02). No other measures were statistically significantly different. In a study of 35 patients injected with 115 sessions of botulinum toxin A in the most problematic site of their tics, the mean peak effect was 2.8 on a 0 to 4 clinical rating scale (0, no improvement, to 4, marked improvement in both severity and function). The mean latency to onset of benefit was 3.8 days (maximum, 10 days). Twenty-one (84%) of 25 patients with premonitory sensations noted benefit for these symptoms. The results from these two studies are insufficient to determine botulinum toxin's efficacy in the treatment of tics.

**Chronic daily headache:**
Four studies were published in the American Academy of Neurology's 2008 assessment of
botulinum neurotoxin for pain disorders. Each of the studies specifically referenced chronic daily headache (CDH) and had a large population of patients with transformed migraine. The primary outcome measure for all the studies was mean change in headache-free days per month. The first study, which used a technique of modifying injection site based on location of pain, showed a significant benefit (11 days vs. 8 days) in the BoNTA treated population. The second study, the largest of patients with CDH, was a randomized, double-blind, placebo-controlled, phase II study, enrolling 702 patients. This trial used a fixed-site strategy. Eligible patients were injected with BoNTA at 225 U, 150 U, 75 U, or placebo and returned for additional masked treatments at day 90 and day 180. Patients were assessed every 30 days for 9 months. The primary efficacy end point was the mean change from baseline in frequency of headache-free days at day 180 for the placebo nonresponder group. The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed with BoNTA at 225 U, 150 U, 75 U, or placebo, respectively (p=0.44). However, a priori-defined analysis of headache change from baseline in headache frequency revealed that the 225 U and 150 U Botox A groups had statistically significant greater reductions in headache frequency compared with placebo at day 240 (p=0.03). In conclusion, BoNTA was safe and well tolerated. Although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240, but the placebo response was higher than expected. The third study was a subgroup of patients not taking prophylactic medications from a larger overall study. Only this subgroup showed a significant mean increase in headache-free days although there was a decrease in the frequency per 30 days. An additional study evaluated 82 patients with chronic daily headache treated with botulinum neurotoxin A. 76.1% of the chronic migraine patients and 36.4% of the chronic tension-type headache patients were considered responders. Because studies of botulinum A for the prevention of chronic daily headache show mixed results, further studies are recommended.

Tension headache:
Four studies of patients with tension-type headache were reviewed in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders. Patients in these studies were randomized to either botulinum neurotoxin (BoNT) or placebo. After 6 weeks, the first study (n = 112) showed no significant difference compared to a baseline 6 week period in the primary outcome measure of area under the headache curve in the subjects' headache diary. In another of the studies, both the BoNT and the placebo group showed improvement in the primary outcome of mean change from baseline in number of headache-free days from 30 to 60 after injection, but BoNT was not more beneficial and a power analysis was not provided. A third study showed no significant benefit of BoNT after 12 weeks for decrease of headache intensity on visual analog scale, mean number of headache days, headache hours per day, days on which symptomatic treatment was taken, number of analgesics taken per day, or patient's assessment of improvement. The fourth study, a smaller trial, included 16 patients in a prospective double-blind, placebo-controlled crossover study and thirty patients in an open-label long-term study. These patients showed reduction in headache severity and pericranial muscle tenderness, and increased headache-free days with botulinum treatment.

In a double-blind, placebo-controlled trial BTX-A was studied in the treatment of tension headache in 21 patients. Efficacy measures included analgesic consumption, pain intensity, site and duration of headache, impression of improvement on a clinical global impression scale (CGI), muscle tenderness and pain, and quality of life surveys. These were assessed at baseline and again 4, 8, and 12 weeks post-injection. Improvement from baseline was noted in both the BTX-A and placebo groups in pain intensity and the CGI, but no statistically significant differences were noted between groups. The only statistically significant difference between groups was in the Everyday-Life Questionnaire that found significant differences in favor of placebo at 4 weeks (p=0.047) and 12 weeks (p=0.009). In another double-blind, placebo-controlled trial the efficacy of BTX-A was assessed in the treatment of chronic headache due to a whiplash injury. Outcome
measures were assessed at baseline and 2 and 4 weeks post-injection and included subjective head pain based on visual analog scales and an objective assessment of range of motion. At baseline patients randomized to the BTX-A group had significantly higher pain scores than the placebo group (6.5 vs. 3.0, p<0.01). At 2 weeks there was a trend toward improvement in both measures in the BTX-A group but no change in the placebo group. At 4 weeks, the BTX-A showed significant improvements vs. baseline in pain scores (6.5 vs. 3.5, p<0.01) and range of motion (312 degrees vs. 343 degrees, p<0.01). It was not reported if there were any significant differences between BTX-A and placebo at any time.

In a double-blind, randomized trial the efficacy of BTX-A was compared to placebo in the treatment of tension headaches in 60 patients.61 At randomization, each patient completed the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) and was asked to record the intensity of headache, daily activities, feelings of depression, tension and anger on a self-rating visual analog scale (VAS). After 4 weeks, patients again completed the WHYMPI and received bilateral injections in the frontal muscles and temporal superficial muscles with either 20 U BTX-A or placebo per injection. The primary efficacy measure was the pain severity ratings from both the WHYMPI and VAS. No statistically significant difference could be found between the groups using either measure. There was no statistically significant difference in the percentage of patients who responded to treatment, defined as a 25% reduction in pain intensity, between the groups. The only statistically significant difference between the groups was found at 4 weeks in the affective score on WHYMPI and angry mood on the VAS.

In another randomized, double-blind trial, the safety and efficacy of BTX-A was compared to placebo in the treatment of chronic tension-type headache.103 Thirty-seven patients were randomized to receive 100 units of BTX-A (n = 22) or placebo (n=15) injected into the temporal and cervical muscles in each side of the head. Patients kept a daily diary beginning 1 month prior to injection and for 3 months post injection. Headache intensity, rated on a 6 point scale, analgesic use, and any other pertinent information related to headaches was recorded. After treatment, the BTX-A group showed steady, statistically significant improvements in headache severity over the 3 months of the study (p=0.002). At 3 months the BTX-A group had a significant improvement in the number of headache free days compared to the baseline period (p=0.001). There also was a numerically greater number of patients treated with BTX-A that had a greater than 25% improvement in headache symptoms scores (13/22 vs. 2/15 in the placebo group, no p value given). No serious side effects were reported during the trial.

Additional small randomized controlled trials have found conflicting results similar to those presented above.128,176-8 Until larger randomized trials are conducting showing a beneficial effect of BTX-A, its use in tension headache is unproven.

**Migraine headache:**
Four studies of patients with episodic migraines treated with BoNT were published in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders.138 One randomized, double-blind study included 232 patients with four to eight moderate to severe migraines per month. This study compared BoNTA to placebo and was powered to detect a difference of 2 headaches per month difference between groups. A statistical significance was not seen between the groups at 1 to 3 months after injection.958

The second study included 3 sequential controlled investigations with re-randomization of 418 patients with a dosing range of 7.5 to 50 units. Patients’ baseline was four to eight moderate to severe migraines per month. Both BoNTA and placebo produced a comparable result in decrease from baseline in frequency between 1 to 4 months. There were no statistically significant, consistent, between group differences.169

The third study was a double-blind, vehicle-controlled study of 123 patients with a history of 2 to 8
moderate to severe headaches per month. Patients were randomized to vehicle only, 25 U BTX-A, or 75 U BTX-A. During a 1 month baseline period and for 3 months post-injection, patients recorded in a daily diary migraine frequency, severity and associated symptoms. There were statistically significant improvements in the BTX-A 25 U group vs. vehicle in the reduction of moderate to severe migraine headaches at 2 months (-1.57 vs. -0.37, p=0.008) and 3 months (-1.88 vs. -0.98, p=0.042) and in all migraines at 3 months (-2.12 vs. -0.9, p=0.014). There were also significantly more patients who had 2 fewer migraines per month and more patients had at least a 50% reduction in the frequency of migraines at 3 months in the 25 U BTX-A group vs. vehicle. At months 1 and 2, the 25U group had significant improvement in the severity of migraine headaches and at month 3 experienced fewer migraine-associated symptoms than the vehicle group. At month 2 both the 25 U and 75 U BTX-A had significant improvements in Subject Global Assessment scores vs. vehicle (BTX-A 25 U, 1.19; BTX-A 75 U, 1.25; vehicle 0.46; p<0.041).

The fourth study, a double-blind, randomized, placebo-controlled study, included sixty patients with migraine according to criteria of the International Headache Society. The patients were randomly assigned to receive either placebo in the frontal and neck muscles, or to receive 16 U botulinum toxin A in the frontal muscles and placebo in the neck muscles, or to receive a total of 100 U botulinum toxin A in the frontal and neck muscles. The observational period was 3 months. In both treatment groups, 30% of patients showed a reduction of migraine frequency in month 3 by at least 50% compared with baseline, in the placebo group 25% of the patients showed such a reduction (P=0.921). There were no significant differences between the three study groups with respect to reduction of migraine frequency, number of days with migraine, and the number of total single doses to treat a migraine attack. In the post hoc analysis, the reduction of all accompanying symptoms was significantly higher in the 16 U treatment group compared with the placebo group. A significantly higher number of adverse events occurred in the 100 U treatment group compared with the placebo group. All adverse events were mild and transient. This study did not show any efficacy of botulinum toxin A in the prophylactic treatment of migraine.

Other migraine studies included an open-label trial in which 106 patients with migraine headache were treated with BTX-A. Patients enrolled either had received BTX-A injections for hyper-functional facial lines or sought treatment with BTX-A for migraine headaches. Of the 106 patients, 77 were classified as having migraine headaches according to the International Headache Society Criteria for Migraine. In the 77 patients with migraine headache treated prophylactically, 51% had complete resolution of their headaches. Patients with less frequent headaches or less severe headaches tended to have complete resolution of their headaches more often than those with higher frequency or severity. Ten subjects with an acute migraine headache were treated with BTX-A and 7 had complete resolution of their headaches in 1 to 2 hours. In another open label trial, 24 of 29 patients who were injected with BTX-A in the corrugator supercilii muscles had a beneficial effect on their migraine headaches.

Two additional randomized, double-blind, placebo-controlled exploratory studies (n=495 and n=369) of botulinum toxin type A in the treatment of episodic migraine showed no statistically significant difference in improvement versus placebo. Other small studies utilizing botulinum toxin for migraine have been conducted.

A meta-analysis of eight randomized, double-blind, placebo-controlled trials also concluded that botulinum toxin A for the prophylactic treatment of episodic migraine headaches was not significantly different from placebo, both from a clinical and statistical perspective.

**Miscellaneous:**

Botulinum toxin A has been studied in a number of other disorders including: cricopharyngeal dysphagia, gustatory epiphora (crocodile tears), Sphincter of Oddi dysfunction, pancreas divisum, anismus, lower urinary tract dysfunction, pelvic floor spasticity, chronic prostatic pain, severe paradoxical
vocal cord movement, postparotidectomy sialoceles, severe bruxism, temporomandibular disorders, myofascial pain syndrome, brachial plexus palsy, thyroid associated ophthalmopathy, esophageal spasm, post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia, trismus and stridor in amyotrophic lateral sclerosis, proctalgia fugax, nasal hypersecretion, gastroparesis (including diabetic gastroparesis), Lichen simplex, lateral epicondylitis, Stiff-person syndrome, benign prostatic hyperplasia, traumatic sixth nerve palsy, Tourette's syndrome, and pain and/or wound healing after hemorrhoidectomy.

The studies in these disorders have been small and/or uncontrolled open-label trials. Larger, well-designed studies must occur to demonstrate the effectiveness of botulinum toxin in the treatment of these conditions.

Technology Assessments:
A 2011 Cochrane review was published evaluating botulinum toxin injections for low back pain and sciatica. Authors included three randomized trials (n=123 patients). Only one study included patients with chronic non-specific LBP; the other two examined unique subpopulations. Only one of the three trials had a low risk of bias and demonstrated that BoNT injections reduced pain at three and eight weeks and improved function at eight weeks better than saline injections. The second trial showed that BoNT injections were better than injections of corticosteroid plus lidocaine or placebo in patients with sciatica attributed to piriformis syndrome. The third trial concluded that BoNT injections were better than traditional acupuncture in patients with third lumbar transverse process syndrome. Both studies with high risk of bias had several key limitations. Heterogeneity of the studies prevented meta-analysis. There is low quality evidence that BoNT injections improved pain, function, or both better than saline injections and very low quality evidence that they were better than acupuncture or steroid injections. Future trials should standardize patient populations, treatment protocols and comparison groups, enlist more participants and include long-term outcomes, cost-benefit analysis and clinical relevance of findings.

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for chronic tension-type headache dated December 30, 2011. A relatively large number of well-designed, randomized, placebo-controlled trials (RCTs) have evaluated the effects of botulinum toxin A (BTX-A) on patients diagnosed with chronic tension-type headache (CTTH). The majority of these studies found no benefit of BTX-A relative to placebo. The two studies that did report beneficial effects of BTX on headache frequency and intensity were very small. Overall, BTX-A was safe. None of the studies compared BTX-A with other prophylactic treatments for CTTH. An annual review of the Hayes Directory on January 1, 2014 resulted in no changes to the original findings.

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for migraine headache dated September 22, 2011. Although a relatively large number of well-designed randomized controlled trials (RCTs) have evaluated onabotulinumtoxinA (onaBTX-A) and abobotulinumtoxinA (aboBTX-A) for prevention of migraine, the clinical role of this treatment remains to be established. Many of the available placebo-controlled RCTs found that BTX-A did not provide statistically significant benefits or found that the benefits obtained were inconsistent, for instance, occurring at some time points but not at others. In contrast, the largest available RCT and one of the older RCTs found that patients who underwent treatment with onaBTX-A experienced statistically significant improvements such as reductions in migraine frequency and severity. This divergence in study results cannot be resolved based solely on differences in study size and a more likely explanation was that the benefits obtained with onaBTX-A were relatively small, perhaps too small to be clinically significant. Moreover, due to lack of long-term follow-up, the available RCTs do not provide any data concerning the durability of potential benefits from treatment with onaBTX-A. In addition, there was insufficient evidence to support conclusions regarding the efficacy of onaBTX-A relative to other types of medication for prevention of migraine. Likewise, there was very limited evidence regarding the effectiveness of
aboBTX-A, and no evidence regarding other types of BTX, for the management of chronic or recurrent headache. Therefore, Hayes has assigned a D rating (no proven benefit and/or not safe) to abobotulinumtoxinA for prevention of migraine and to rimabotulinumtoxinB as a treatment for migraine headache. Overall, onaBTX-A was safe with few serious complications reported, earning onabotulinumtoxinA a Hayes rating of C (potential but unproven benefit) for prevention of migraine headache. Further studies are needed to determine the clinical role of BTX-A relative to current treatments for prevention of migraine. An annual review of the Hayes Directory on October 15, 2013 resulted in no changes to the original findings.

Hayes has compiled a Medical Technology Directory on trigger point injections (TPI) for myofacial pain on December 24, 2013. The literature search identified a total of 17 peer-reviewed randomized controlled studies comparing TPIs with placebo or an active control. Based upon these findings, the investigators concluded that TPIs improve pain and may improve function temporarily in patients with myofascial pain, but these effects appear to be unrelated to the substance that is injected. TPI with local anesthetics improves pain compared with no treatment, but not compared with placebo TPI, suggesting that the injection procedure itself and/or patient expectations rather than the anesthetic provide pain relief.

Professional Societies:
In 2008, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U) assessments on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain, movement disorders, and spasticity. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society also published an evidence-based review of the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy in 2010. Recommendations from these reviews are:

- BoNT should be offered as a treatment option for axillary hyperhidrosis and detrusor overactivity (detrusor hyperreflexia) (Level A – Established as effective, ineffective, or harmful for the given condition in the specified population).
- BoNT should be considered for palmar hyperhidrosis, drooling, and detrusor sphincter dyssynergia after spinal cord injury (Level B – Probably effective, ineffective, or harmful for the given condition in the specified population).
- BoNT may be considered for gustatory sweating and low back pain (Level C – Possibly effective, ineffective, or harmful for the given condition in the specified population).
- BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B).
- Evidence does not permit drawing conclusions on BoNT’s efficacy in chronic daily headache (mainly transformed migraine) (Level U – Data inadequate or conflicting; given current knowledge, treatment is unproven).
- BoNT should be offered as an option for the treatment of cervical dystonia (Level A).
- BoNT may be offered for blepharospasm, focal upper extremity dystonia, adductor laryngeal dystonia, and upper extremity essential tremor (Level B).
- BoNT may be considered for hemifacial spasm, focal lower limb dystonia, and motor tics (Level C).
- BoNT should be offered as an option for the treatment of spasticity in adults (Level A). Spasticity in adults results from a variety of causes such as stroke, trauma, multiple sclerosis, and neoplasm involving the central nervous system.
- For localized/segmental spasticity that warrants treatment in children and adolescents with cerebral palsy, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A) and there is insufficient data to support or refute the use of botulinum toxin type B (Level U).
For non-cosmetic use, onabotulinumtoxinA (Botox) is FDA approved for the prophylaxis of headaches in adult patients with chronic migraine (215 days per month with headache lasting 4 hours a day or longer). Safety and effectiveness of onabotulinumtoxinA (Botox) have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month).  

OnabotulinumtoxinA is also approved for treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis). It is also indicated for reducing the severity of abnormal head position and neck pain associated with cervical dystonia in adults; for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above; for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response or are intolerant to an anticholinergic medication; for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication; and for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.  

RimabotulinumtoxinB (Myobloc) is FDA approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. 

For non-cosmetic use, abobotulinumtoxinA (Dysport) is FDA approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients. 

IncobotulinumtoxinA (Xeomin) is FDA approved for the treatment of adults with cervical dystonia to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients. IncobotulinumtoxinA is also indicated for the treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA (Botox).  

**APPLICABLE CODES**

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. 

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ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2015*, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.

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<td>N31.1</td>
<td>Reflex neuropathic bladder, not elsewhere classified</td>
</tr>
<tr>
<td>N31.9</td>
<td>Neuromuscular dysfunction of bladder, unspecified</td>
</tr>
<tr>
<td>N32.81</td>
<td>Overactive bladder</td>
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<tr>
<td>N36.44</td>
<td>Muscular disorders of urethra</td>
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<tr>
<td>N39.41</td>
<td>Urge incontinence</td>
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<tr>
<td>N39.46</td>
<td>Mixed incontinence</td>
</tr>
<tr>
<td>R25.0</td>
<td>Abnormal head movements</td>
</tr>
<tr>
<td>R25.1</td>
<td>Tremor, unspecified</td>
</tr>
<tr>
<td>R25.2</td>
<td>Cramp and spasm</td>
</tr>
<tr>
<td>R25.3</td>
<td>Fasciculation</td>
</tr>
<tr>
<td>R25.8</td>
<td>Other abnormal involuntary movements</td>
</tr>
<tr>
<td>R25.9</td>
<td>Unspecified abnormal involuntary movements</td>
</tr>
<tr>
<td>R29.891</td>
<td>Ocular torticollis</td>
</tr>
<tr>
<td>R49.0</td>
<td>Dysphonia</td>
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<tr>
<td>R49.9</td>
<td>Unspecified voice and resonance disorder</td>
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<tr>
<td>S04.50XA</td>
<td>Injury of facial nerve, unspecified side, initial encounter</td>
</tr>
<tr>
<td>S04.51XA</td>
<td>Injury of facial nerve, right side, initial encounter</td>
</tr>
<tr>
<td>S04.52XA</td>
<td>Injury of facial nerve, left side, initial encounter</td>
</tr>
</tbody>
</table>

**REFERENCES**


Botulinum Toxins A and B: Drug Policy (Effective 09/01/2014)
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70. Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients


### POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
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<tbody>
<tr>
<td>9/1/2014</td>
<td>Policy revised per annual review. Added general instructions for medical necessity review. Revised medical necessity criteria for the treatment of cervical dystonia to include symptoms of pain and/or functional impairment. Revised onabotulinumtoxinA criteria for the prevention of migraine headaches. Updated clinical evidence and references. Updated list of ICD-9 codes (added 378.82) and associated ICD-10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 7/8/2014. Policy 2014D0017M archived.</td>
</tr>
<tr>
<td>8/16/2010</td>
<td>Policy revised per annual review. Added spasticity associated with spinal cord injury as proven for botulinum toxin type A. Added ICD-9 codes 333.89, 343.3, 343.4, and 343.9. Approved by the National Pharmacy &amp; Therapeutics Committee on 7/12/2010. Policy 2010D0017G archived.</td>
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**Botulinum Toxins A and B: Drug Policy (Effective 09/01/2014)**

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<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>11/16/2009</td>
<td>Policy revised with changes to Coverage Rationale: spasticity associated with traumatic brain injury and neurogenic detrusor hyperreflexia added as proven for botulinum toxin type A; sialorrhea and neurogenic detrusor hyperreflexia added as proven for botulinum toxin type B; specified that botulinum toxin type A is proven for detrusor-sphincter dyssynergia due to spinal cord injury or disease, but unproven for detrusor-sphincter dyssynergia due to multiple sclerosis. Added ICD-9 codes 784.42 and 596.54 and removed 784.49. Added Dysport to the policy. Approved by National Pharmacy &amp; Therapeutics Committee on 6/9/2009. Policy 2008D0017E archived.</td>
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<tr>
<td>3/12/2008</td>
<td>ICD 9 Codes added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.</td>
</tr>
<tr>
<td>10/21/2005</td>
<td>HCPCS codes added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.</td>
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