INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

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 United Healthcare 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 member specific benefit plan document must be reviewed to determine what benefits, if any, exist for treatment of hyperhidrosis.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan 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.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small
group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

**COVERAGE RATIONALE**

This policy refers to the following drug products:

**Botulinum toxin types A and B:**
- Dysport® (abobotulinumtoxinA)
- Xeomin® (incobotulinumtoxinA)
- Botox® (onabotulinumtoxinA)
- Myobloc® (rimabotulinumtoxinB)

The following information pertains to medical necessity review:

**General Requirements (applicable to all medical necessity requests)**

I. For initial therapy, both of the following:
   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 and

II. 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 and

III. Botulinum toxin administration is no more frequent than every 12 weeks, regardless of diagnosis.

**Diagnosis-Specific Requirements**

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

I. **Dysport (abobotulinumtoxinA) is proven in the treatment of the following conditions:**
   A. Achalasia
      - Dysport is medically necessary for the treatment of achalasia when all of the following criteria are met:
         1. Diagnosis of achalasia as confirmed by esophageal manometry; and
         2. Patient has failed or is not a candidate for pneumatic dilation or myotomy; and
         3. History of failure, contraindication, or intolerance to one of the following:
            a. Calcium channel blocker
            b. Long-acting nitrate
               and
         4. Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy.

   B. Anal fissures, chronic
      - Dysport is medically necessary for the treatment of chronic anal fissures when all of the following criteria are met:
         1. Diagnosis of chronic anal fissure; and
         2. At least 2 months of symptoms including one of the following:
            a. Nocturnal pain and bleeding
            b. Postdefecation pain
               and
         3. History of failure, contraindication, or intolerance to one of the following conventional therapies:
            a. Topical nitrate
            b. Topical calcium channel blocker (e.g., diltiazem, nifedipine)

   C. Blepharospasm associated with dystonia

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D. Cervical dystonia (also known as spasmodic torticollis)\textsuperscript{10,19,81,83,84}  

**Dysport is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:**

1. Diagnosis of cervical dystonia; and  
2. Symptoms including both of the following:  
   a. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment  
   b. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)  

E. Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease\textsuperscript{15,17,18,53,54,63,81}  

**Dysport is medically necessary when both of the following criteria are met:**

1. **One** of the following:  
   a. Diagnosis of detrusor overactivity  
   b. Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease and  
2. History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine)  

F. Hand dystonia (writer's, musician's or typist's cramp)\textsuperscript{19,81,83}  
G. Hand tremor\textsuperscript{19,81}  
H. Hemifacial spasm (seventh cranial nerve disorders)\textsuperscript{19,81}  
I. Hyperhidrosis\textsuperscript{1,15,81} including gustatory sweating (Frey's Syndrome)\textsuperscript{9,15,38}  
J. Oromandibular dystonia  
K. Sialorrhea\textsuperscript{15,57,81}  
L. Spasmodic dysphonia (laryngeal dystonia)\textsuperscript{319}  
M. Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord\textsuperscript{1,6,39,81}  
N. Strabismus\textsuperscript{1,19,81}  
O. Tongue dystonia  
P. Torsion dystonia  
Q. Voice tremor\textsuperscript{4}  

II. **Xeomin** (incobotulinumtoxinA) is proven in the treatment of the following conditions:  

A. Blepharospasm associated with dystonia, defined by both of the following:\textsuperscript{70,76}  
   1. Diagnosis of blepharospasm associated with dystonia; and  
   2. History of failure, contraindication, or intolerance to Botox (onabotulinumtoxinA)  

B. Cervical dystonia (spasmodic torticollis)\textsuperscript{70,76,83-4}  

**Xeomin is medically necessary for the treatment of cervical dystonia (spasmodic torticollis) when both of the following criteria are met:**

1. Diagnosis of cervical dystonia; and  
2. Symptoms including both of the following:  
   a. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment  
   b. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)  

C. Sialorrhea\textsuperscript{70}  
D. Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord\textsuperscript{55-6,70,76}  

III. **Botox** (onabotulinumtoxinA) is proven in the treatment of the following conditions:  

A. Achalasia\textsuperscript{80}  

**Botox is medically necessary for the treatment of achalasia when all of the following criteria are met:**

1. Diagnosis of achalasia as confirmed by esophageal manometry; and  
2. Patient has failed or is not a candidate for pneumatic dilation or myotomy; and  
3. History of failure, contraindication, or intolerance to one of the following:  
   a. Calcium channel blocker  
   b. Long-acting nitrate and  
4. Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy.
B. Anal fissures, chronic\textsuperscript{8,80}

**Botox is medically necessary for the treatment of chronic anal fissures when all of the following criteria are met:**
1. Diagnosis of chronic anal fissure; and
2. At least 2 months of symptoms including one of the following:
   a. Nocturnal pain and bleeding
   b. Post defecation pain
   and
3. History of failure, contraindication, or intolerance to one of the following conventional therapies:
   a. Topical nitrates
   b. Topical calcium channel blockers (e.g., diltiazem, nifedipine)

C. Blepharospasm associated with dystonia\textsuperscript{1,19,80}

D. Cervical dystonia (also known as spasmodic torticollis)\textsuperscript{1,10,80,83-4}

**Botox is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:**
1. Diagnosis of cervical dystonia; and
2. Symptoms including both of the following:
   a. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
   b. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

E. Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease\textsuperscript{15,17,18,53,54,63,80}

**Botox is medically necessary when both of the following criteria are met:**
1. One of the following:
   a. Diagnosis of detrusor overactivity
   b. Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease
   and
2. History of failure, contraindication, or intolerance to two anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine)

F. Hand dystonia (writer's, musician's or typist's cramp)\textsuperscript{19,80,83}

G. Hand tremor\textsuperscript{19,80}

H. Hemifacial spasm (seventh cranial nerve disorders)\textsuperscript{19,80}

I. Hyperhidrosis\textsuperscript{1,80} including gustatory sweating (Frey's Syndrome)\textsuperscript{9,15,38}

J. Migraine headache, chronic\textsuperscript{1,71,80} 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

**Botox is medically necessary for the prophylaxis of chronic migraine when all of the following criteria are met:**
1. Diagnosis of chronic migraine, 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
   and
2. 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:
   a. Antidepressant [i.e., Elavil (amitriptyline), Effexor (venlafaxine)]
   b. Antiepileptic drug [i.e., Depakote/Depakote ER (divalproex sodium), Topamax (topiramate)]
   c. Beta blocker [i.e., atenolol, Inderal (propranolol), nadolol, timolol, Toprol XL (metoprolol extended-release)]
   and
3. OnabotulinumtoxinA dose does not exceed 155 units administered intramuscularly divided over 31 injection sites divided across 7 head and neck muscles every 12 weeks

K. Oromandibular dystonia
L. Overactive bladder

**Botox is medically necessary for the treatment of overactive bladder when all of the following criteria are met:**
1. Diagnosis of overactive bladder; and
2. **One** of the following symptoms:
   a. Urge urinary incontinence
   b. Urgency
   c. Frequency
   **and**
3. History of failure, contraindication, or intolerance to **two** anticholinergic medications (e.g., oxybutynin, tropicamid, darifenacin, tolterodine)
   **and**
4. OnabotulinumtoxinA dose does not exceed 100 units divided over 20 injection sites every 12 weeks

M. Sialorrhea

N. Spasmodic dysphonia (laryngeal dystonia)

O. Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord

P. Strabismus

Q. Tongue dystonia

R. Torsion dystonia

S. Voice tremor

IV. **Myobloc (rimabotulinumtoxinB) is proven in the treatment of the following conditions:**

A. Cervical dystonia (also known as spasmodic torticollis)

**Myobloc is medically necessary for the treatment of cervical dystonia when both of the following criteria are met:**
1. Diagnosis of cervical dystonia; and
2. Symptoms including **both** of the following:
   a. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
   b. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

B. Detrusor overactivity (also known as detrusor hyperreflexia)

**Myobloc is medically necessary when both of the following criteria are met:**
1. Diagnosis of neurogenic detrusor overactivity; and
2. History of failure, contraindication, or intolerance to **two** anticholinergic medications (e.g., oxybutynin, tropicamid, darifenacin, tolterodine)

C. Sialorrhea

D. Spasticity associated with cerebral palsy; multiple sclerosis; neuromyelitis optica (NMO); stroke; or other injury, disease, or tumor of the brain or spinal cord

Unproven

Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of chronic migraine headache.

Botox, Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of the following conditions:
- Acquired nystagmus
- Anismus (pelvic floor dyssynergia)
- Benign prostatic hyperplasia
- Brachial plexus palsy
- Chronic daily headache
- Chronic low back pain
- Chronic prostatic pain
- Cricopharyngeal dysphagia
- Epiphora following salivary gland transplantation
- Esophageal spasm
- Gastroparesis (including diabetic gastroparesis)
- Gustatory epiphora (Crocodile tears)
- Head tremor
- Lateral epicondylitis (tennis elbow)

Botulinum Toxins A and B
UnitedHealthcare Commercial Medical Benefit Drug Policy

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• Lichen simplex
• Lower urinary tract (voiding) dysfunction\textsuperscript{11,18}
• Motor tics
• Myofascial pain syndrome\textsuperscript{45,72,81}
• Nasal hypersecretion\textsuperscript{50,67}
• Pain and/or wound healing after hemorrhoidectomy
• Pancreas divisum
• Pelvic floor spasticity (and associated pain conditions)\textsuperscript{18}
• Piriformis syndrome\textsuperscript{69}
• Postparotidectomy sialoceles
• Post-thoracotomy pseudoangina
• Proctalgia fugax\textsuperscript{18}
• Severe bruxism\textsuperscript{41-42}
• Severe paradoxical vocal cord movement\textsuperscript{40}
• Sphincter of Oddi dysfunction\textsuperscript{12}
• Stiff-person syndrome
• Temporomandibular disorders\textsuperscript{42-44,48}
• Tension headache\textsuperscript{13,27,78}
• Thyroid associated ophthalmopathy\textsuperscript{17}
• Tourette's syndrome\textsuperscript{56}
• Traumatic sixth nerve palsy
• Trigeminal neuralgia\textsuperscript{32,73-4}
• Trismus and stridor in amyotrophic lateral sclerosis

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

For non-cosmetic use, abobotulinumtoxinA (Dysport) is FDA approved for the treatment of adults with cervical dystonia. Dysport is also indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors, wrist flexors and finger flexors. Dysport is also indicated for the treatment of lower limb spasticity in pediatric patients 2 years of age and older.\textsuperscript{10}

IncobotulinumtoxinA (Xeomin) is FDA approved for the treatment of adults with cervical dystonia in both botulinum toxin-naive and previously treated patients. Xeomin is also indicated for the treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA (Botox). Xeomin is also indicated for the treatment of upper limb spasticity in adult patients and chronic sialorrhea.\textsuperscript{70}

For non-cosmetic use, onabotulinumtoxinA (Botox) is FDA approved for the prophylaxis of headaches in adult patients with chronic migraine (\textgteq;15 days per month with headache lasting 4 hours a day or longer). Safety and effectiveness of Botox have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month).\textsuperscript{1} Botox 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), finger flexors (flexor digitorum profundus and flexor digitorum sublimis), and thumb flexors (adductor pollicis and flexor pollicis longus). Botox is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus). Safety and effectiveness of Botox have not been established for the treatment of other upper or lower limb muscle groups. Safety and effectiveness of Botox have not been established for the treatment of spasticity in pediatric patients under age 18 years. Botox has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with Botox is not intended to substitute for usual standard of care rehabilitation regimens.\textsuperscript{1}

Botox 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 of 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.\textsuperscript{1} Safety and efficacy of Botox for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive Botox for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease. Safety and effectiveness of Botox have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.
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.\(^2\)

All botulinum toxin products approved by the FDA carry a black box warning regarding the possibility of the distant spread of toxin effect.\(^1,2,10,70\) The warning states that post marketing reports indicate that the effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses.

**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.\(^1,2,10,70\)

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.\(^1,2,10,70\)

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

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**ICD-10 Diagnosis Code** | **Description**
---|---
R25.0 | Abnormal head movements
R25.1 | Tremor, unspecified
R25.2 | Cramp and spasm
R25.3 | Fasciculation
R25.8 | Other abnormal involuntary movements
R25.9 | Unspecified abnormal involuntary movements
R29.891 | Ocular torticollis
R49.0 | Dysphonia
R49.9 | Unspecified voice and resonance disorder
S04.50XA | Injury of facial nerve, unspecified side, initial encounter
S04.51XA | Injury of facial nerve, right side, initial encounter
S04.52XA | Injury of facial nerve, left side, initial encounter

**CLINICAL EVIDENCE**

**Proven**

**Cervical Dystonia**

In a randomized, double-blind, multicenter, non-inferiority, two-period crossover study, Yun et al compared the efficacy and safety of Dysport and Botox at a 2.5:1 ratio in the treatment of cervical dystonia (CD). The lower ratio than 3:1 was suggested as a more appropriate conversion ratio, due to the higher efficacy of Botox and more frequent incidence of adverse effects in CD and other focal movement disorders. Patients who were over 20 years old and have experienced CD for at least 18 months were eligible, and were allowed to continue on a stable dose of medications for CD for the duration of the trial. Both products were diluted so that the 2.5:1 ratio resulted in the same volume to be administered. The patients received either Dysport or Botox, and were followed monthly for the first 16 weeks. After the 4 week washout period, each group was crossed over to receive the other product, respectively. Patients were also followed up with monthly for 16 weeks in the second period. Results from both periods were merged and compared according to the two different products. The primary efficacy outcome was the change in the Tsui scale between the baseline value and that at 1 month after each injection (peak effect). One hundred and two patients enrolled in the study. Patients were allocated 49 and 53 to two different arms of the trial. Arm 1 received Dysport during the first phase and Botox during the crossover phase. Arm 2 received Botox during the first phase and Dysport during the second phase. Only 94 of the 102 patients completed the entire study and were included in the final analysis. Mean changes in the Tsui scale between baseline and 4 weeks after each injection trended to favor Botox, however, this was not statistically significant (4.0 ± 3.9 points Dysport vs. 4.8 ± 4.1 points for Botox; 95% CI, -0.1 – 1.7; p = 0.091). The mean change of the Toronto western spasmodic torticollis rating scale score, the proportion of improvement in clinical global impression and patient global impression, and the incidences of adverse events were not significantly different between the two treatments. The authors concluded that, in terms of efficacy and safety, Dysport at a ratio of 2.5:1 to Botox was not inferior to Botox in patients with CD.

**Detrusor Overactivity**

In a prospective, long-term (3 year), multicenter, open-label extension study following a 52-week, phase III trial of onabotulinumtoxinA, patients were treated on an “as needed” basis with intradetrusor onabotulinumtoxinA (200U or 300U) for urinary incontinence (UI) due to neurogenic detrusor overactivity. Patients received treatment ≥ 12 weeks since the previous treatment and a UI episode threshold. The primary efficacy endpoint was the change from study baseline in UI episodes/day at week 6 after each treatment. Additional efficacy measurements included: percent change in UI episodes, the proportions of patients with ≥ 50% and 100% reductions from baseline in UI episodes/day, changes from baseline in volume/void and Incontinence Quality of Life (I-QOL) total summary scores, I-QOL responder rates (proportion of patients achieving a ≥ 11-point increase from baseline in I-QOL total score, which is defined as the minimally important difference for I-QOL in NDO), and duration of treatment effect (time to patient request for retreatment). OnabotulinumtoxinA 200U consistently reduced UI episodes/day; reductions from baseline ranged from −3.2 to −4.1 across six treatments. Volume/void consistently increased, nearly doubling after treatment. I-QOL improvements were consistently greater than twice the minimally important difference (+11 points). Overall median duration of effect was 9.0 months (200U). Results were similar for onabotulinumtoxinA 300U. Most common AEs were urinary tract infections and urinary retention. De novo CIC rates were 29.5, 3.4, and 6.0% (200U), and 43.0, 15.0, and 4.8% (300U) for treatments 1–3, respectively; de novo CIC rates were 0% for treatments 4–6. The authors concluded that OnabotulinumtoxinA treatments consistently improve UI, volume/void, and QOL in patients with UI due to NDO in this 4-year study, with no new safety signals.
Migraine Headache

OnabotulinumtoxinA is beneficial for the prophylaxis of chronic migraine headaches based upon FDA approval, published practice guidelines, professional society evidence reviews, randomized controlled clinical trials, and smaller randomized exploratory studies.15,24,25-6

Aurora et al performed a secondary analysis of the data to assess patients who received all five treatment cycles and completed the PREEMPT-1 and PREEMPT-2 trials. Both studies were 24 week double-blind, placebo controlled, parallel-group phase, with a 32-week open-label phase, that evaluated the efficacy and safety of onabotulinumtoxinA (BoNT-A). Out of a total of 1,384 total patients, 1,005 received all five treatment cycles and were included in the analysis. Of these, 513 received all 5 cycles with BTA, whereas 492 underwent 2 cycles of placebo followed by 3 cycles of BoNT-A treatment. After 56 weeks of treatment, significant between group differences were found favoring BoNT-A treatment vs. placebo, even after those receiving placebo switching to BoNT-A. The following headache symptoms were evaluated: mean change in frequency of headache days (-12.0 vs -11.0, p=0.035); total migraine days (-11.6 vs -10.7, p=0.038), and moderate/severe headache days (-11.0 vs -10.1 n=0.042). There were also large mean improvements from baseline in the following measures: cumulative hours of headache on headache days, frequency of headache episodes, percentage with severe Headache Impact Test (HIT)-6 scores, and total HIT-6 and Migraine-Specific Quality of Life Questionnaire scores. The percent of patients with a ≥ 50% reduction from baseline in frequency of headache days was significantly greater for the BoNT-A only group at week 56 (69.6% vs 62.8%, p = 0.023). Treatment-related adverse event rates were 28.5% for the BoNT-A 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 supports the use of onabotulinumtoxinA for the treatment of migraine headaches.

In a follow up analysis of the PREEMPT clinical trials, Lipton et al., assessed the effects of treatment with onabotulinumtoxinA on health-related quality of life (HRQoL) and headache impact in adults with chronic migraine.28

In the PREEMPT trials, Headache Impact Test (HIT)-6 scores were obtained at baseline and every 4 weeks. In terms of change in total HIT-6 scores, a negative value reflects reduced headache impact and an improvement in the patient’s functionality. HRQoL was measured by the Migraine-Specific Quality of Life Questionnaire (MSQ v2.1). This score was obtained at baseline and every 12 weeks. A positive change in MSQ v2.1 scores reflects improvement in HRQoL during the PREEMPT study. An analysis of the combined data looked at 688 subjects who received treatment with Botox vs. 696 who received saline placebo injections. Baseline mean total HIT-6 and MSQ v2.1 scores were comparable between groups; 93.1% were severely impacted based on HIT-6 scores ≥ 60. At 24 weeks, in comparison with placebo, Botox treatment significantly reduced HIT-6 scores at all time periods during the double-blind phase of the trials (p<0.014). Additionally, HIT-6 measures of headache impact scores showed significant benefit for the Botox group at 24 weeks of treatment (p<0.001). Botox treatment significantly improved all domains of the MSQ v2.1 at 24 weeks (p<0.001). There was also 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=0.025). The authors concluded that Botox treatment reduces headache impact and improves HRQoL.

The pooled results of two phase 3, randomized, double-blind, multicenter, placebo controlled trials addressing the use of botulinum toxin for the treatment of chronic migraine headaches were reported by Dodick et al., in 2010.29-31 These studies were from the Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program, involving a 24 week randomized, double-blind phase followed by a 32 week open-label phase. Subjects were randomized (1:1) to receive either 155 units of onabotulinumtoxinA (BoNT-A) or placebo injections every 12 weeks. A total of 1384 adult patients were randomized to onabotulinumtoxinA (n=688) or placebo (n=696), with study visits every 4 weeks. Both studies were identical in design, with the exception being the designation of the primary (mean change from baseline in frequency of headache days for the 28-day period ending with week 24) and secondary endpoints (frequency of migraine days, number of cumulative hours of headache on headache days, proportion of patients with severe HIT-6 score, and others). Injections of BoNT-A or placebo were injected as 31 fixed-sites, fixed-dose injections across 7 specific head/neck muscle areas. A discretionary 40 units could be administered using a “follow-the-pain” strategy, resulting in 195 units over 39 sites. 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 was 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. The authors concluded that the use of onabotulinumtoxinA treatment for chronic migraine was effective, safe, and well tolerated.
**Overactive Bladder**

Nitti et al examined the efficacy and safety of onabotulinumtoxinA for the treatment of overactive bladder and urinary incontinence (UI) in a phase 3, randomized, multicenter, placebo controlled trial. Adult patients (18 years or older) with idiopathic overactive bladder who experienced 3 or more urgency UI episodes in a 3-day period and an average of 8 or more micturitions per day were enrolled in the study. Patients were randomized 1:1 to either receive onabotulinumtoxinA 100 U or placebo over 20 evenly distributed intradetrusor injections. Co-primary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the treatment benefit scale at posttreatment week 12. Secondary end points included other overactive bladder symptoms and health related quality of life. OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (-2.65 vs -0.87, p <0.001) and 22.9% vs 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA than placebo treated patients reported a positive response on the treatment benefit scale (60.8% vs 29.2%, p <0.001). All other overactive bladder symptoms improved vs placebo (p <0.05). OnabotulinumtoxinA improved patient related quality of life across multiple measures (p <0.001). Uncomplicated urinary tract infection was the most common adverse event. A 5.4% rate of urinary retention was observed. The authors concluded that OnabotulinumtoxinA showed significant, clinically relevant improvement in all overactive bladder symptoms and health related quality of life in patients inadequately treated with anticholinergics and was well tolerated.

**Spasticity (associated with cerebral palsy)**

In a global, randomized, placebo-controlled study, the efficacy and safety of abobotulinumtoxinA was evaluated for the treatment of spasticity in cerebral palsy children with dynamic equinus foot deformity. Two hundred and forty-one patients were randomized 1:1:1 to receive either abobotulinumtoxinA 10 U/kg/leg, 15 U/kg/leg, or placebo injections into the gastrocnemius–soleus complex of either one or both legs. The primary endpoint was the demonstration of benefit for each dose over placebo on the Modified Ashworth Scale from baseline to week 4. Secondary endpoint includes the change of the Physician’s Global Assessment at week 4 from baseline. Two hundred and twenty-six patients completed the study. At week 4, Modified Ashworth Scale scores significantly improved with abobotulinumtoxinA; mean (95% confidence interval) treatment differences versus placebo were -0.49 (-0.75 to -0.23; P = 0.0002) for 15 U/kg/leg and -0.38 (-0.64 to -0.13; P = 0.003) for 10 U/kg/leg. The Physician’s Global Assessment treatment differences versus placebo of 0.77 (0.45 to 1.10) for 15 U/kg/leg and 0.82 (0.50 to 1.14) for 10 U/kg/leg were also significant (both Ps < .0001). The most common treatment-related adverse event was muscular weakness (10 U/Kg/leg = 2; placebo = 1). The authors concluded that treatment with abobotulinumtoxinA improves muscle tone in children with dynamic equinus resulting in an improved overall clinical impression and is well tolerated.

**Unproven**

**Benign Prostatic Hyperplasia**

The efficacy and tolerability of botulinum toxin A (BoNT-A) for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (LUTS/BPH) was evaluated in a randomized placebo controlled trial involving 315 subjects assigned to either 200 U of BoNT-A (Botox) (n=157) or placebo (n=156). Patients with International Prostate Symptom Score (I-PSS) 14 or greater, with peak urinary flow rate 4 to 15 ml per second and total prostate volume 30 to 80 ml were randomized 1:1 to a single intraprostatic injection of BoNT-A or placebo. A single-blind sham procedure, followed by a 4 week run in was included to minimize potential placebo effect. The primary endpoint from baseline is total I-PSS at week 12. Additional endpoints assessed at weeks 6, 12, and 24 were peak urinary flow rate (Qmax), total prostate volume (TPV), and post-void residual urine volume (PVR). At all time points there was no difference in I-PSS between the BoNT-A and placebo groups, included at the primary time point at 12 weeks, however both groups experienced a decrease (-6.3 vs -5.6 points, p <.001). There were no differences between treatment groups for TPV, PSA, or PVR at 12 or 24 weeks. The authors concluded that BoNT-A is unlikely to be a therapy for male LUTS/BPH.

**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 the 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 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.15 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.5 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.

Additional small randomized controlled trials have found conflicting results similar to those presented above.27 Until larger randomized trials are conducting showing a beneficial effect of BTX-A, its use in tension headache is unproven.

**Miscellaneous**

Botulinum toxin A has been studied in a number of other disorders including: cricopharyngeal dysphagia,20-23 gustatory toxidromes (crocodile tears), Sphincter of Oddi dysfunction,12 pancreas divisum, anismus,16 lower urinary tract dysfunction,11,18 pelvic floor spasticity,18 chronic prostatic pain,18 severe paradoxical vocal cord movement,40 postparotidectomy sialoceles, severe bruxism,41-42 temporomandibular disorders,43-44 myofascial pain syndrome,45,48,71 brachial plexus palsy,46,80,81,86,90 thyroid associated ophthalmopathy,47 esophageal spasm,37 post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia,43,44,73-75 trismus and stridor in amyotrophic lateral sclerosis, proctalgia fugax,18 nasal hypersecretion,30,87 gastroparesis (including diabetic gastroparesis),48,62,80,81,91 Lichen simplex, lateral epicondylitis,51,52 Stiff-person syndrome, traumatic sixth nerve palsy, Tourette's syndrome,55 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**

**Achalasia**

A 2014 Cochrane review was published evaluating and comparing endoscopic pneumatic dilation (PD) versus botulinum toxin injection in the management of primary achalasia.34 Seven studies involving 178 participants were included. Two studies were excluded from the meta-analysis of remission rates on the basis of clinical heterogeneity of the initial endoscopic protocols. There was no significant difference between PD or botulinum treatment in remission within four weeks of the initial intervention; with a risk ratio of remission of 1.11 (95% CI 0.97 to 1.27). There was also no significant difference in the mean esophageal pressures between the treatment groups; with a weighted mean difference for PD of -0.77 (95% CI -2.44 to 0.91, P = 0.37). Data on remission rates following the initial endoscopic treatment were available for three studies at six months and four studies at 12 months. At six months 46 of 57 PD participants were in remission compared to 29 of 56 in the botulinum group, giving a risk ratio of 1.57 (95% CI 1.19 to 2.08, P = 0.0015); whilst at 12 months 55 of 75 PD participants were in remission compared to 27 of 72 botulinum participants, with a risk ratio of 1.88 (95% CI 1.35 to 2.61, P = 0.0002). No serious adverse outcomes occurred in participants receiving botulinum, while PD was complicated by perforation in three cases. The authors concluded that PD is the more effective endoscopic treatment in the long term (greater than six months) for patients with achalasia.

**Chronic Migraine Headache**

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for migraine headache dated September 22, 2011.75 Although a relatively large number of well-designed randomized controlled trials (RCTs) have evaluated onabotulinumtoxinA (onaBTX-A) and abobotulinumtoxinA (aboBTX-A) [BTX-A] for prevention of migraine, the clinical

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**Botulinum Toxins A and B**

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**Effective 10/01/2018**
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 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 August 26, 2015 resulted in no changes to the original findings.

**Chronic Tension Headache**

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for chronic tension-type headache dated December 30, 2011.78 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 13, 2015 resulted in no changes to the original findings.

**Detrusor Overactivity**

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for detrusor instability, dated December 30, 2011.86 The results of the available studies provide some evidence that onabotulinumtoxinA (onaBTX-A) improves outcomes for patients who have idiopathic or neurogenic detrusor overactivity; however, these studies do not provide sufficient evidence to establish the clinical role of botulinum toxin type A (BTX-A) for these indications. Although randomized clinical trials (RCTs) consistently found that BTX-A provided statistically significant improvements in urinary incontinence (UI) compared with placebo treatment, the largest available RCT of BTX-A for idiopathic detrusor overactivity found a placebo effect that was nearly as large as the treatment effect when expressed in terms of decrease in number of episodes of UI per week. In the largest available RCT of BTX-A for neurogenic detrusor overactivity, BTX-A treatment was associated with statistically significant increases in urinary retention and urinary tract infections. None of the studies that met the criteria for review involved long-term follow-up of patients who underwent treatment with multiple doses of BTX-A, and none of the studies compared BTX-A with augmentation cystoplasty or neuromodular implantation. At least six of the studies were sponsored by the manufacturer, creating the potential for bias. Additional controlled studies are needed to determine the long-term efficacy and safety of BTX-A relative to other current invasive treatments for idiopathic and neurogenic detrusor overactivity. An annual review of the Hayes Directory on January 9, 2015 resulted in no changes to the the original findings.

**Strabismus**

A 2012 Cochrane review was published evaluating botulinum toxin injections for the treatment of strabismus.35 The authors included 4 randomized controlled trials in their analysis. Two trials found that there was no difference between the use of botulinum toxin and surgery for patients requiring retreatment for acquired esotropia or infantile esotropia. There was no evidence for a prophylactic effect of botulinum toxin in a treatment trial of acute onset sixth nerve palsy. Botulinum toxin had a poorer response than surgery in a trial of patients requiring treatment for horizontal strabismus in the absence of binocular vision. It was not possible to establish dose effect information. Complication rates for use of Botox® or Dysport® ranged from 24% to 55.54%.72

**Professional Societies**

**Achalasia**

In 2013, the American College of Gastroenterology published an evidence-based clinical guideline for the diagnosis and management of achalasia based on a comprehensive review of the pertinent evidence and examination of relevant published data.85 The recommendations for the treatment of achalasia from this guideline are as follows:

- Either graded pneumatic dilation (PD) or laparoscopic surgical myotomy with a partial fundoplication are recommended as initial therapy for the treatment of achalasia in those fit and willing to undergo surgery (strong recommendation, moderate-quality evidence).
• PD and surgical myotomy should be performed in high-volume centers of excellence (strong recommendation, low-quality evidence).
• The choice of initial therapy should be guided by patients’ age, gender, preference, and local institutional expertise (weak recommendation, low-quality evidence).
• Botulinum toxin therapy is recommended in patients who are not good candidates for more definitive therapy with PD or surgical myotomy (strong recommendation, moderate quality evidence).
• Pharmacologic therapy for achalasia is recommended for patients who are unwilling or cannot undergo definitive treatment with either PD or surgical myotomy and have failed botulinum toxin therapy (strong recommendation, low-quality evidence).

**Autonomic & Movement Disorders, Pain, & Spasticity**

In a 2013 update to the 2008 Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) 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. In addition, in 2013 authors performed an assessment on the use of botulinum neurotoxin in the treatment of urologic conditions and secretory disorders based on the AAN methodology. 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 classified as follows:
• Level A - Established as effective, ineffective, or harmful for the given condition in the specified population, requiring at least two consistent Class I studies.
• Level B - Probably effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class I study or at least two consistent Class II studies.
• Level C - Possibly effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class II study or two consistent Class III studies.
• Level U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Recommendations from these reviews are:
• BoNT should be offered as a treatment option for axillary hyperhidrosis and detrusor overactivity (Level A). BoNT should be considered for palmar hyperhidrosis, sialorrhea, and detrusor sphincter dyssynergia after spinal cord injury (Level B).
• BoNT is probably effective for the treatment of benign prostatic hyperplasia induced lower urinary tract symptoms (Level B).
• BoNT may be considered for low back pain (Level C). 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). Evidence does not support BoNT’s efficacy for the treatment of gustatory sweating (Level U).
• BoNT should be offered as an option for the treatment of blepharospasm, cervical dystonia (Level A).
• BoNT may be offered for hemifacial spasm, focal upper extremity dystonia, and upper extremity essential tremor (Level B).
• BoNT may be considered for adductor laryngeal dystonia, focal lower limb dystonia, oromandibular 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).

**Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache**

In a 2016 update to the 2008 guidelines, the American Academy of Neurology (AAN) published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U) assessments on the use of botulinum neurotoxins in the treatment of blepharospasm, cervical dystonia, headache, and adult spasticity.

Recommendations from this review are classified as follows:
• Level A - Established as effective, ineffective, or harmful for the given condition in the specified population, requiring at least two consistent Class I studies.
• Level B - Probably effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class I study or at least two consistent Class II studies.
• Level C - Possibly effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class II study or two consistent Class III studies.
• Level U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Recommendations from this review for abobotulinumtoxinA (aboBoNT-A, Dysport) are as follows:
• AboBoNT-A should be offered as a treatment option for cervical dystonia, focal manifestations of upper limb spasticity, and focal manifestations of lower limb spasticity that warrant treatment (Level A).
  o AboBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies). AboBoNT-A has also been established as safe and effective for the reduction of adult lower limb spasticity (multiple Class I studies).
  o Data is inadequate to determine the efficacy of aboBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes). Data is also inadequate to determine the efficacy of aboBoNT-A for improvement of active function associated with adult lower limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple Class I studies).
• AboBoNT-A may be considered as a treatment option for blepharospasm (Level C).

Recommendations from this review for incobotulinumtoxinA (incoBoNT-A, Xeomin) are as follows:
• IncoBoNT-A should be offered as a treatment option for focal manifestations of upper limb spasticity (Level A).
  o IncoBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies).
  o Data is inadequate to determine the efficacy of incoBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes).
• IncoBoNT-A should be considered as a treatment option for blepharospasm and cervical dystonia (Level B).
• There is insufficient evidence to support or refute the use of incoBoNT-A for the treatment of lower limb spasticity (Level U).

Recommendations from this review for onabotulinumtoxinA (onaBoNT-A, Botox) are as follows:
• OnaBoNT-A should be offered as a treatment option for focal manifestations of upper limb spasticity, focal manifestations of lower limb spasticity that warrant treatment, and chronic migraine (Level A).
  o OnaBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies). OnaBoNT-A has also been established as safe and effective for the reduction of adult lower limb spasticity (multiple Class I studies).
  o Data is inadequate to determine the efficacy of onaBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes). Data is also inadequate to determine the efficacy of onaBoNT-A for improvement of active function associated with adult lower limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple Class I studies).
• OnaBoNT-A should be considered as a treatment option for blepharospasm and cervical dystonia (Level B).
• OnaBoNT-A should not be offered as a treatment option for episodic migraine (Level A).
• OnaBoNT-A should not be considered as a treatment option for tension-type headache (Level B).

Recommendations from this review for rimabotulinumtoxinB (rimaBoNT-B, Myobloc) are as follows:
• RimaBoNT-B should be offered as a treatment option for cervical dystonia (Level A).
• RimaBoNT-B should be considered as a treatment option for focal manifestations of upper limb spasticity (Level B).
  o RimaBoNT-B is probably safe and effective for the reduction of adult upper limb spasticity (1 Class I study).
  o Data is inadequate to determine the efficacy of rimaBoNT-B for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes).
• There is insufficient evidence to support or refute the use of rimaBoNT-B for the treatment of blepharospasm and lower limb spasticity (Level U).

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

National Coverage Determinations (NCDs) do not exist for botulinum toxins at this time. Local Coverage Determinations (LCDs) do exist; see the LCDs for Botulinum Toxin Type A & Type B, Botulinum Toxin Types A and B, Botulinum Toxin Types A and B Policy, Botulinum Toxins, Chemodenervation and Drugs and Biologicals: Botulinum Toxins.

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 August 11, 2017)
REFERENCES

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| 10/01/2018 | - Updated list of applicable ICD-10 diagnosis codes to reflect annual code edits:  
  - Added G51.31, G51.32, G51.33, and G51.39  
  - Removed G51.3  
  - Archived previous policy version 2018D0017T                                                                                                                                                                           |
<p>| 09/01/2018 | Off cycle review. Added coverage for Xeomin for sialorrhea. Updated references. Approved by the National Pharmacy and Therapeutics Committee on 08/17/2018. Policy 2018D0017S archived.                                                                |
| 01/01/2018 | Annual review. Updated coverage rationale, CMS statement, clinical evidence, and references. Approved by the National Pharmacy and Therapeutics Committee on 11/17/2017. Policy 2017D0017R archived.        |
| 01/01/2017 | Policy revised per annual review. Moved policy to new template. Updated coverage rationale to include for types A and B. Added additional coverage criteria for the use of Xeomin in blepharospasm per package insert. Updated spasticity coverage to include additional ICD10 codes (G04.1, G11.4). Added spasticity to coverage criteria for Myobloc. Included the diagnosis of neuromyelitis optica (NMO) for criteria that includes multiple sclerosis and added corresponding ICD10 code (G36.0). Removed Piriformis syndrome from coverage and removed corresponding ICD 10 codes (M54.30, M54.31, M54.32, M54.40, M54.41, M54.42, G57.00, G57.01, G57.02, G57.03). Removed evidence for chronic low back pain and myofascial pain syndromes. Updated FDA information, updated list of ICD-10 codes for spasticity (added G04.1, G11.4), updated clinical evidence and CMS statement. Removed language to indicate ICD-10-CM (diagnoses) and ICD-10-PCS (inpatient procedures) must be used to report diagnoses for services provided on or after 10/01/2015. Updated references and formatting. Approved by the National Pharmacy and Therapeutics Committee on 10/26/2016. Policy 2015D0017Q archived. |
| 10/01/2015 | Updated Applicable Codes for ICD-10 transition. Policy 2014D0017N archived                                                                                                                                                                |
| 09/01/2014 | 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 07/08/2014. Policy 2014D0017M archived. |
| 02/01/2014 | Policy revised. Removed Xeomin dosing criterion for cervical dystonia. Approved by the National Pharmacy &amp; Therapeutics Committee on 12/13/2013. Policy 2013D0017L archived.                                                                     |
| 10/01/2013 | Policy revised per annual review. Coverage Rationale reformatted to list each botulinum toxin individually. Added OAB to the list of proven indications for onabotulinumtoxinA. Revised medical necessity criteria for migraine prophylaxis. Added medical necessity criteria for cervical dystonia, chronic anal fissure, detrusor overactivity and detrusor sphincter dyssynergia due to spinal cord injury or disease. Updated FDA section to include new indication for onabotulinumtoxinA (treatment of overactive bladder). Updated list of ICD-9 codes (added 596.51, 788.31, 788.33, and 951.4; removed 781.7) and associated ICD-10 codes. Approved by the National Pharmacy &amp; Therapeutics Committee on 07/09/2013. Policy 2012D0017K archived. |
| 09/01/2012 | Policy revised per annual review. Clinical evidence and references updated. Added Cochrane review on low back pain. Added Hayes Medical Technology Directory on tension-type headache. Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/2014. |</p>
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<th>Date</th>
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<tbody>
<tr>
<td>01/01/2012</td>
<td>Approved by the National Pharmacy &amp; Therapeutics Committee on 07/10/2012. Policy 2012D0017J archived. Policy revised. Removed detrusor-sphincter dyssynergia due to multiple sclerosis from the list of unproven uses for botulinum toxin type A. Added Hayes Medical Technology Directory on migraine headache. Updated FDA section to include new indication for onabotulinumtoxinA (treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition). Replaced code Q2040 with code J0588, which becomes effective on 01/01/2012. Approved by the National Pharmacy &amp; Therapeutics Committee on 11/08/2011. Policy 2011D0017I archived.</td>
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<tr>
<td>09/01/2011</td>
<td>Policy revised per annual review. Added trigeminal neuralgia to the list of unproven uses. Added Hayes Medical Technology Directory on gastroparesis. Updated list of proven ICD-9 codes (added 351.9 and 724.3; removed 333.1, 340, and 350.1). Clinical Evidence and References updated. Approved by the National Pharmacy &amp; Therapeutics Committee on 07/12/2011. Policy 2010D0017G archived.</td>
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<tr>
<td>03/25/2011</td>
<td>Policy updated with addition of code Q2040, which becomes effective on 04/01/2011.</td>
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| 08/16/2010 | • 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 & Therapeutics Committee on 05/11/2010.  
• Policy revised to change spasticity associated with traumatic brain injury or spinal cord injury to spasticity associated with other injury, disease, or tumor of the brain or spinal cord. Added Professional Societies section. Approved by the National Pharmacy & Therapeutics Committee on 08/11/2010. Policy 2009D0017F archived. |
| 11/16/2009 | 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 & Therapeutics Committee on 06/09/2009. Policy 2008D0017E archived. |
| 09/10/2008 | Policy revised with changes in the coverage rationale. Approved by National Pharmacy & Therapeutics Committee on 06/10/2008. Policy 2007D0017D archived.                                                                                                                                                                                            |
| 03/12/2008 | ICD 9 Codes added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.                                                                                                                                                                                                                                                                                   |