The services described in Oxford policies are subject to the terms, conditions and limitations of the Member's contract or certificate. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage enrollees. Oxford reserves the right, in its sole discretion, to modify policies as necessary without prior written notice unless otherwise required by Oxford's administrative procedures or applicable state law. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

Certain policies may not be applicable to Self-Funded Members and certain insured products. Refer to the Member's plan of benefits or Certificate of Coverage to determine whether coverage is provided or if there are any exclusions or benefit limitations applicable to any of these policies. If there is a difference between any policy and the Member's plan of benefits or Certificate of Coverage, the plan of benefits or Certificate of Coverage will govern.

## CONDITIONS OF COVERAGE

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¹ Precertification always required for inpatient admission
² Precertification with Medical Director review is required
Special Considerations

1. Precertification is required for services covered under the Member's General Benefits Package when performed in the office of a participating provider. Precertification is not required, but encouraged, for out of network services performed in the office that are covered under the Member's General Benefits Package. If precertification is not obtained, Oxford may review for medical necessity after the service is rendered.

2. Review by a Medical Director or their designee is required for all ICD-9 diagnosis codes not listed in the Applicable Codes section of this policy.

COVERAGE RATIONALE

This policy refers to the following drug products:

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

**Botulinum toxin type B**
- Myobloc® (rimabotulinumtoxinB)

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

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

**DYSPORT**

Dysport is proven and medically necessary in the treatment of the following conditions:

1. **Achalasia**

Botulinum Toxins A and B: Clinical Policy (Effective 04/01/2016)
Additional information to support medical necessity review:
Dysport is medically necessary for the treatment of achalasia when all of the following criteria are met:

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

2. Anal fissures, chronic

Additional information to support medical necessity review:
Dysport 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:
   (1) Nocturnal pain and bleeding
   (2) Post defecation pain
   and

c. History of failure, contraindication, or intolerance to one of the following conventional therapies:
   (1) Topical nitrate
   (2) Topical calcium channel blocker (e.g., diltiazem, nifedipine)

3. Blepharospasm associated with dystonia

4. Cervical dystonia (also known as spasmodic torticollis)

Additional information to support medical necessity review:
Dysport 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)

5. 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:
Dysport 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)

6. **Hand dystonia (writer’s, musician’s or typist’s cramp)**

7. **Hand tremor**

8. **Hemifacial spasm (seventh cranial nerve disorders)**

9. **Hyperhidrosis** including gustatory sweating (Frey’s Syndrome)

10. **Oromandibular dystonia**

11. **Piriformis syndrome**

12. **Sialorrhea**

13. **Spasmodic dysphonia (laryngeal dystonia)**

14. Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or tumor of the brain or spinal cord

15. **Strabismus**

16. **Tongue dystonia**

17. **Torsion dystonia**

18. **Voice tremor**

**XEOMIN**

Xeomin is proven and medically necessary in the treatment of the following conditions:

1. **Blepharospasm associated with dystonia**

2. **Cervical dystonia (spasmodic torticollis)**

   Additional information to support medical necessity review:
   Xeomin 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 tumor of the brain or spinal cord**

**BOTOX**

Botox is proven and medically necessary in the treatment of the following conditions:

1. **Achalasia**

   Additional information to support medical necessity review:
   Botox is medically necessary for the treatment of achalasia when all of the following criteria are met:
   
   a. Diagnosis of achalasia as confirmed by esophageal manometry; and
   
   b. Patient has failed or is not a candidate for pneumatic dilation or myotomy; and
   
   c. History of failure, contraindication, or intolerance to one of the following:

   (1) Calcium channel blocker

   (2) Long-acting nitrate

   and

   d. Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy
2. Anal fissures, chronic

Additional information to support medical necessity review:
Botox 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:
   (1) Nocturnal pain and bleeding
   (2) Postdefecation pain
   and
   c. History of failure, contraindication, or intolerance to two of the following conventional therapies:
      (1) Topical nitrates
      (2) Topical calcium channel blockers (e.g., diltiazem, nifedipine)

3. Blepharospasm associated with dystonia

4. Cervical dystonia (spasmodic torticollis)

Additional information to support medical necessity review:
Botox 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)

5. 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:
Botox 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)

6. Hand dystonia (writer’s, musician’s or typist’s cramp)

7. Hand tremor

8. Hemifacial spasm (seventh cranial nerve disorders)

9. Hyperhidrosis including gustatory sweating (Frey’s Syndrome)

10. Migraine headache, chronic

Additional information to support medical necessity review:

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
Botox 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:
   (1) Antidepressant [i.e., Elavil (amitriptyline), Effexor (venlafaxine)]
   (2) Antiepileptic drug [i.e., Depakote/Depakote ER (divalproex sodium), Topamax (topiramate)]
   (3) Beta blocker [i.e., atenolol, Inderal (propranolol), nadolol, timolol, Toprol XL (metoprolol extended-release)]
   and
c. OnabotulinumtoxinA dose does not exceed 155 units administered intramuscularly divided over 31 injection sites divided across 7 head and neck muscles every 12 weeks

11. Oromandibular dystonia
12. Overactive bladder

Additional information to support medical necessity review:
Botox 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)
   and
d. OnabotulinumtoxinA dose does not exceed 100 units divided over 20 injection sites every 12 weeks

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

MYOBLOC

Myobloc is proven and medically necessary in the treatment of the following conditions:

1. Cervical dystonia (also known as spasmodic torticollis)

Additional information to support medical necessity review:
Myobloc 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)

2. Detrusor overactivity (also known as detrusor hyperreflexia)\textsuperscript{138,142,146}

Additional information to support medical necessity review:
Myobloc 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)

3. Sialorrhea\textsuperscript{116,138,267-9}

\textbf{UNPROVEN/NOT MEDICALLY NECESSARY INDICATIONS}

Dysport, Xeomin, and Myobloc are unproven and not medically necessary in the treatment of chronic migraine headache.\textsuperscript{34-5,131-2,138,168-9,170-1,108-7,281,296,303}

Botox, Dysport, Myobloc, and Xeomin are unproven and NOT medically necessary in the treatment of the following conditions:

1) Acquired nystagmus\textsuperscript{18-20,172-3}
2) Anismus (pelvic floor dyssynergia)\textsuperscript{51,78,139,140}
3) Benign prostatic hyperplasia\textsuperscript{109,130,146,185,285,302,303}
4) Brachial plexus palsy\textsuperscript{69,70,237-8,302,303}
5) Chronic daily headache\textsuperscript{133-135,138,179,188,302,303}
6) Chronic low back pain\textsuperscript{60,138,302}
7) Chronic prostatic pain\textsuperscript{73,146}
8) Cricopharyngeal dysphagia\textsuperscript{42,64-5,148-64}
9) Epiphora following salivary gland transplantation\textsuperscript{77}
10) Esophageal spasm\textsuperscript{74,199-1}
11) Gastroparesis (including diabetic gastroparesis)\textsuperscript{99,90,98,145,270-7,302}
12) Gustatory epiphora (Crocodile tears)\textsuperscript{138,193-5}
13) Head tremor\textsuperscript{14-15}
14) Lateral epicondylitis (tennis elbow)\textsuperscript{95,248-51}
15) Lichen simplex\textsuperscript{54}
16) Lower urinary tract (voiding) dysfunction\textsuperscript{71,88,122-3,146}
17) Motor tics\textsuperscript{62,169}
18) Myofascial pain syndrome\textsuperscript{59,75,96,226-36,290,303}
19) Nasal hypersecretion\textsuperscript{83,247,284}
20) Pain and/or wound healing after hemorrhoidectomy\textsuperscript{125,265-6}
21) Pancreas divisum\textsuperscript{72}
22) Pelvic floor spasticity (and associated pain conditions)\textsuperscript{146,291}
23) Postparotidectomy sialoceles\textsuperscript{56}
24) Post-thoracotomy pseudoangina\textsuperscript{75}
25) Proctalgia fugax\textsuperscript{62,146,292}
26) Severe bruxism\textsuperscript{97,90,205-12}
27) Severe paradoxical vocal cord movement\textsuperscript{65,204}
28) Sphincter of Oddi dysfunction\textsuperscript{50,102,200-3}
29) Stiff-person syndrome\textsuperscript{97,254}
30) Temporomandibular disorders\textsuperscript{58,213-25,243}
31) Tension headache\textsuperscript{32-33,61,103,127-9,138,174-8,299}
32) Thyroid associated ophthalmopathy\textsuperscript{73,239-42}
33) Tourette’s syndrome\textsuperscript{24,189,261-4}
Botulinum toxin type A and B are considered cosmetic when used to improve appearance, or in the absence of physiological functional impairment that would be improved by their use. Most Oxford Certificates of Coverage (COCs) exclude benefit coverage for cosmetic services. Some plans may exclude benefit coverage for medical and surgical treatment of excessive sweating (hyperhidrosis). The member 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 member 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. Refer to: Acquired Rare Disease Drug Therapy Exception Process.

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 (such as maternity benefits), 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 guideline, it is important to refer to the member specific benefit document to determine benefit 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

Proven/Medically Necessary

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).\(^{131}\) 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 spasmotic 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.

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.44,132,138,168,169,170

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.35 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.180 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
Acquired nystagmus

The use of BTX-A for the treatment of acquired nystagmus was studied in an open-label trial involving 6 patients.\(^\text{18}\) 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.\(^\text{19}\)

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.\(^\text{20}\) 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 report\(^\text{172}\) 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.\(^\text{173}\) The horizontal component of the nystagmus was eliminated for

Unproven/Not Medically Necessary
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.

**Benign Prostatic Hyperplasia**

The efficacy and tolerability of botulinumtoxin 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).\(^6\) 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 <0.001). 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.\(^6\) 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.\(^7\) The second study, the largest of patients with CDH, was a randomized, double-blind, placebo-controlled, phase II study, enrolling 702 patients.\(^5\) 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.\(^5\) 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.\(^6\) 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.

**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.\(^6\) 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.
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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 OLBQP (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.

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.\textsuperscript{127} 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.\textsuperscript{32} 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.\textsuperscript{33} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{128,176-8} 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,\textsuperscript{42,64-5,146-64} gustatory epiphora (crocodile tears),\textsuperscript{42,57,193-5} Sphincter of Oddi dysfunction,\textsuperscript{72} anisms,\textsuperscript{51,78,138,140} lower urinary tract dysfunction,\textsuperscript{71,86,122-3,146} pelvic floor spasticity,\textsuperscript{71,140} chronic prostatic pain,\textsuperscript{55,204} severe paradoxical vocal cord movement,\textsuperscript{55,204} postparotidectomy sialoceles,\textsuperscript{56} severe bruxism,\textsuperscript{57,60,205-12} and 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, gastroesophageal reflux disease (including diabetic gastroparesis), lateral epicondylitis, Stiff-person syndrome, traumatic sixth nerve palsy, Tourette's syndrome, and pain and/or wound healing after hemorroidectomy.

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. 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 Low Back Pain
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.

Chronic Migraine Headache
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 (BTX-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 onabotulinumtoxinA 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 onabotulinumtoxinA. In addition, there was insufficient evidence to support conclusions regarding the efficacy of onabotulinumtoxinA relative to other types of medication for prevention of migraine. Likewise, there was very limited evidence regarding the effectiveness of abobotulinumtoxinA, 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 (abobotulinumtoxinA) for prevention of migraine and to rimabotulinumtoxinB as a treatment for migraine headache. Overall, onabotulinumtoxinA 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 September 16, 2014 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. 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. 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 17, 2014 resulted in newly published studies; however, there were no changes to the conclusions of the original findings.

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for chronic anal fissure, dated December 22, 2010. Overall, the results of 13 randomized clinical trials on botulinum toxin (BTX) treatment for chronic anal fissures (CAF) in adults suggest that BTX is safe, and is associated with moderate to high healing rates and pain reduction, but also with high recurrence rates. Although BTX treatment was associated with healing of anal fissures and pain reduction in all studies, healing rates varied substantially across studies. In studies comparing BTX with sphincterotomy, BTX was associated with lower healing rates and higher recurrence rates. However, BTX is not associated with permanent side effects, while sphincterotomy may lead to permanent fecal incontinence in some patients. Studies comparing BTX with topical treatments yielded contradictory results. An annual review of the Hayes Directory on November 4, 2014 resulted in newly published studies, however, there were no changes to the conclusions of the original findings.
**Myofascial Pain Syndromes**

A 2014 Cochrane review was published evaluating botulinum toxin injection for myofascial pain syndromes (MPS) in adults. This was an update from the previous review in 2012. Four studies were included with a total of 233 participants, comparing botulinum with placebo. In one study with 145 participants, significant improvement rates of pain intensity scores and duration of daily pain were demonstrated when comparing botulinum with placebo. The three other studies showed that there was no statistically significant difference between botulinum and placebo in pain intensity. The authors concluded that there was inconclusive evidence to support the use of botulinum toxin in the treatment of MPS based on data from four studies with a total of 233 participants, which were considered of sufficient quality to be included in this review. Meta-analyses were not possible due to the heterogeneity between studies. The authors suggest that in future studies the same methodology to assess pain, a standardized dose of treatment, follow-up of at least four months (to observe the maximum and minimum curve of the drug effect) and appropriate data presentation should be used. More high-quality trials of botulinum toxin for treating MPS need to be conducted before firm conclusions on its effectiveness and safety can be drawn.

**Strabismus**

A 2012 Cochrane review was published evaluating botulinum toxin injections for the treatment of strabismus. 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%.

**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. The recommendations for the treatment of achalasia from this guideline are:

1. 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).
2. PD and surgical myotomy should be performed in high-volume centers of excellence (strong recommendation, low-quality evidence).
3. The choice of initial therapy should be guided by patients’ age, gender, preference, and local institutional expertise (weak recommendation, low-quality evidence).
4. 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).
5. 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 2010.21

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 (detrusor hyperreflexia) (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).
- 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).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

For non-cosmetic use, onabotulinumtoxinA (Botox) is FDA approved for the prophylaxis of headaches in adult patients with chronic migraine (≥15 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).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). 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.¹

Myobloc is FDA approved² for the treatment of adults with cervical dystonia to reduce the severity
of abnormal head position and neck pain associated with cervical dystonia.²

For non-cosmetic use, Dysport is FDA approved⁸¹ 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.⁸¹

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).²⁸⁸

All botulinum toxin products approved by the FDA carry a black box warning regarding the
possibility of the distant spread of toxin effect.¹,²,⁸¹,²⁸⁸ 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.

APPLICABLE CODES

System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a service
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 enrollee specific benefit 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 claims payment. Other policies and coverage
determination guidelines may apply. This list of codes may not be all inclusive.

Applicable HCPCS Codes

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<tr>
<th>HCPCS Code</th>
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<td>J0585</td>
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<td>J0586</td>
<td>Injection, abobotulinumtoxinA, 5 units (Dysport)</td>
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<td>J0587</td>
<td>Injection, rimabotulinumtoxinB, 100 units (Myobloc)</td>
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<td>J0588</td>
<td>Injection, incobotulinumtoxinA, 1 unit (Xeomin)</td>
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ICD-9 Diagnosis Codes (Discontinued 10/01/15)
The following list of codes is provided for reference purposes only. Effective October 1, 2015, the
Centers for Medicare & Medicaid Services (CMS) implemented ICD-10-CM (diagnoses) and ICD-
10-PCS (inpatient procedures), replacing the ICD-9-CM diagnosis and procedure code sets.

ICD-9 codes will not be accepted for services provided on or after October 1, 2015.

<table>
<thead>
<tr>
<th>ICD-9 Code (Discontinued 10/01/15)</th>
<th>Description</th>
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<td>342.12</td>
<td>Spastic hemiplegia, affecting non-dominant side</td>
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<td>Disturbance of salivary secretion</td>
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<td>596.51</td>
<td>Hypertonicity of bladder</td>
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<td>Neurogenic bladder, NOS</td>
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<td>596.55</td>
<td>Detrusor sphincter dyssynergia</td>
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<td>705.21</td>
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<td>724.3</td>
<td>Sciatica</td>
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<td>ICD-9 Code (Discontinued 10/01/15)</td>
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<tr>
<td>951.4</td>
<td>Injury to facial nerve (seventh cranial nerve)</td>
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</table>

Review by a Medical Director or their designee is required for all ICD-9 diagnosis codes not listed above.

Review by a Medical Director or their designee is required for all ICD-10 diagnosis codes not listed below.

**Additional Search Codes:**
The CPT codes listed below are additional search terms and are for reference purposes only:

1. 64612 - Chemodenervation of muscle(s); muscle(s) innervated by facial nerve (e.g., for blepharospasm, hemifacial spasm)
2. 64650 - Chemodenervation of eccrine glands; both axilla
3. 64653 - Chemodenervation of eccrine glands; other area(s) (e.g., scalp, face, neck), per day
4. 67345 - Chemodenervation of extraocular muscle

**ICD-10 Codes**
ICD-10-CM (diagnoses) and ICD-10-PCS (inpatient procedures) must be used to report services provided on or after October 1, 2015.

**ICD-10 codes will not be accepted for services provided prior to October 1, 2015.**

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<tr>
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<td>Other drug induced dystonia</td>
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<td>Genetic torsion dystonia</td>
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<td>Idiopathic nonfamilial dystonia</td>
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<td>Spasmodic torticollis</td>
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<td>G43.709</td>
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<td>G43.711</td>
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<td>G43.719</td>
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<td>Geniculate ganglionitis</td>
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<td>Melkersson's syndrome</td>
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<td>M54.41</td>
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<td>S04.52XA</td>
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</tbody>
</table>

**REFERENCES**

*The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2015D0017P]*


POLICY HISTORY/REVISION INFORMATION

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<th>Action/Description</th>
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<td>- Revised coverage rationale:</td>
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<tr>
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<td>o Updated medical necessity criteria for use of Dysport for treatment of achalasia; added criterion requiring other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy</td>
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<tr>
<td></td>
<td>o Updated medical necessity criteria for use of Botox for treatment of chronic migraine and overactive bladder;</td>
</tr>
<tr>
<td></td>
<td>▪ Replaced references to “Botox” with generic drug name “OnabotulinumtoxinA”</td>
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<td>Archived previous policy version PHARMACY 105.24 T2</td>
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