| WellMed<br>Doctors helping patients for more than 25 years | **Effective Date:** 10/27/23 | **Revision Date(s):** 10/18/18, 12/06/18, 01/07/20, 02/11/21, 02/18/22, 10/19/23 |
|---|---|---|
| **Department: PHARMACY** | **MMC Review/ Approval Date(s):** 01/14/20; 03/19/21, 03/15/22, 10/25/23 | **Page(s): 25** |

**Policy Number: 008.006**

**Policy Title: Coverage Determination Policy for Botulinum toxin A and B**

- **Botox (OnabotulinumtoxinA); Dysport (AbobotulinumtoxinA); Myobloc (RimabotulinumtoxinB); Xeomin (IncobotulinumtoxinA)**

**Regions:** ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

**Impacted Areas:**

| | |
|---|---|
| ☒ Network Management/Provider Services | ☒ Utilization Management |
| ☐ Member services | ☐ Case management |
| ☐ Quality Management | ☐ Disease management |
| ☐ Credentialing | ☒ Claims |
| ☐ IT | ☐ Human resources |
| ☐ Administration | ☐ Finance |
| ☐ Compliance/delegation | ☒ Pharmacy |
| | ☐ ALL |

**Available LCD/NCD/LCA:** LCD - Botulinum Toxins (L38809)

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Doctors helping patients for more than 25 years

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**Coverage Policy Number:** 008.006

**Line of Business:** Medicare Part B

**Policy Type:** Prior Authorization

## Coverage Determination:

## General Requirements

**Applicable to ALL requests: New Starts/Renewals/Continuations**

**ALL** of the following:

A. Diagnosis
B. Botulinum toxin administration is no more frequent than every 12 weeks, regardless of diagnosis
C. **ONE** of the following:
    I. Prescriber attests dosing is in accordance with the United States Food and Drug Administration (FDA) approved labeling; or
    II. For indications without FDA approved dosing, prescriber attests there is published clinical evidence to support the dosing

## Initial/New Requests

1. WellMed Medical Management will cover **Botox (OnabotulinumtoxinA)** as medically necessary for the following diagnoses:
   A. **Achalasia** when **BOTH** of the following criteria are met:
      I. Diagnosis of achalasia as confirmed by esophageal manometry
      II. Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy
   B. **Chronic anal Fissure** with inadequate response to conservative or pharmacologic treatment
   C. **Blepharospasm associated with dystonia**
   D. **Cervical Dystonia** (also known as spasmodic torticollis)
   E. **Detrusor overactivity (also known as detrusor hyperreflexia) or Detrusor-sphincter dyssynergia due to a spinal cord injury or disease** when the following criteria are met:
      I. Inadequate response to or are intolerant of an anticholinergic medication
      II. **ONE** of the following:
         a. Diagnosis of detrusor overactivity

         **OR**

         b. Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease
   F. **Focal Limb Dystonia**
   G. **Hand tremor** with a high amplitude tremor that disrupts activities of daily living and have had inadequate response to oral pharmacotherapy such as propranolol and primidone
   H. **Hemifacial spasm** (seventh cranial nerve disorders)
   I. **Severe Axillary Hyperhidrosis** that is inadequately managed by topical agents
   J. **Chronic Migraine Headache** when the following criteria are met:
      I. Diagnosis of chronic migraine, defined by **ALL** of the following:
         a. Greater than or equal to 15 headache days per month
         b. Greater than or equal to 8 migraine days per month
         c. Headaches last 4 hours per day or longer
   K. **Oromandibular dystonia**

L. **Overactive bladder** when **ALL** of the following criteria are met:
    I. Diagnosis of overactive bladder in adults who have an inadequate response to or are intolerant of an anticholinergic medication
    II. **ONE** of the following symptoms:
        a. Urge urinary incontinence
        b. Urgency
        c. Frequency
M. **Sialorrhea**
N. **Spasmodic dysphonia**
O. **Spasticity** associated with **ONE** of the following**:**
    I. Cerebral palsy
    II. Multiple sclerosis
    III. Neuromyelitis optica (NMO)
    IV. Stroke
    V. Other injury, disease or tumor of the brain or spinal cord
P. **Strabismus**
Q. **Tongue dystonia**
R. **Torsion dystonia**
S. **Voice tremors**
T. **Laryngeal dystonia (spastic dysphonia) for adductor type (ADSD)**
U. **Simple motor tics** (bothersome) in adults when the benefits of treatment outweigh the risks
V. **Severely disabling or aggressive vocal tics** in adults when the benefits of treatment outweigh the risks

2. WellMed Medical Management will cover **Xeomin (IncobotulinumtoxinA)** as medically necessary for the following diagnoses:
   A. **Blepharospasm associated with dystonia.**
   B. **Cervical Dystonia** (spasmodic torticollis)
   C. **Spasticity** associated with **ONE** of the following**:**
      I. Cerebral palsy
      II. Multiple sclerosis
      III. Neuromyelitis optica (NMO)
      IV. Stroke
      V. Other injury, disease, or tumor of the brain or spinal cord
   D. **Sialorrhea**

3. WellMed Medical Management will cover **Dysport (AbobotulinumtoxinA)** as medically necessary for the following diagnoses:
   A. **Achalasia** when **both** of the following criteria are met:
      I. Diagnosis of achalasia as confirmed by esophageal manometry
      II. Other causes of dysphagia (e.g., peptic stricture, carcinoma, extrinsic compression) ruled out by upper gastrointestinal endoscopy
   B. **Blepharospasm**
   C. **Chronic anal fissures**
   D. **Cervical Dystonia**
   E. **Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to a spinal cord injury or disease** when the following criteria are met:
      I. **ONE** of the following:
         a. Diagnosis of detrusor overactivity

            **OR**

         b. Diagnosis of detrusor-sphincter dyssynergia due to spinal cord injury or disease
   F. **Hand Dystonia** (writer's, musician's or typist's cramp)
   G. **Hand tremor**
   H. **Hemifacial spasm** (seventh cranial nerve disorders)
   I. **Hyperhidrosis including gustatory sweating** (Frey's Syndrome)
   J. **Oromandibular dystonia**
   K. **Sialorrhea**
   L. **Spasmodic dysphonia**
   M. **Spasticity** associated with **ONE** of the following**:**
      I. Cerebral Palsy
      II. Multiple sclerosis
      III. Neuromyelitis optica (NMO)
      IV. Stroke
      V. Other injury, disease, or tumor of the brain or spinal cord
   N. **Strabismus**
   O. **Tongue dystonia**
   P. **Torsion dystonia**
   Q. **Voice tremors**

4. WellMed Medical Management will cover **Myobloc (RimabotulinumtoxinB)** as medically necessary for the following diagnoses:
   A. **Cervical dystonia or Spasmodic torticollis**
   B. **Detrusor overactivity or Detrusor hyperreflexia**
   C. **Spasticity associated with cerebral palsy; MS, Neuromyelitis Optica; Stroke or other injury, disease or tumor of the brain or spinal cord**
   D. **Sialorrhea**

**NOTE:** Wellmed will **NOT** cover Botox, Dysport, Myobloc and Xeomin for cosmetic indications
(e.g. glabellar lines, smoker's lines, crow's feet, laugh lines and aging neck).
**Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of chronic migraine headache.**

**WellMed Medical Management will NOT cover any botulinum toxin products for the treatment of the following conditions, as they have not been proven medically necessary:**

| | |
|---|---|
| Acquired nystagmus | Pancreas divisum |
| Anismus (pelvic floor dyssynergia)[11] | Pelvic floor spasticity (and associated pain conditions)[13] |
| Benign prostatic hyperplasia[12,13,14] | Piriformis syndrome[26] |
| Brachial plexus palsy[15] | Post-parotidectomy sialoceles |
| Chronic daily headache[16,17] | Post-thoracotomy pseudoangina |
| Chronic low back pain[16] | Proctalgia fugax [13] |
| Chronic prostatic pain[18] | Severe bruxism[27] |
| Cricopharyngeal dysphagia[20] | Severe paradoxical vocal cord movement[18] |
| Epiphora following salivary gland transplantation | Sphincter of Oddi dysfunction |
| Esophageal spasm[21] | Stiff-person syndrome |
| Gastroparesis (including diabetic gastroparesis)[22,23] | Temporomandibular disorders[28] |
| Gustatory epiphora (Crocodile tears) | Tension headache[17,29] |
| Head tremor | Thyroid associated ophthalmopathy |
| Lateral epicondylitis (tennis elbow)[25] | Tourette's syndrome[30] |
| Lichen simplex | Traumatic sixth nerve palsy |
| Lower urinary tract (voiding) dysfunction[19,13] | Trigeminal Neuralgia |
| Motor tics | Trismus and stridor in amyotrophic lateral sclerosis |
| Myofascial pain syndrome[24] | |
| Nasal hypersecretion[50,67] | |
| Pain and/or wound healing after hemorrhoidectomy | |

## Renewal/Continuation of Therapy Requests

**ALL Indications:**

1. Botulinum toxin administration is no more frequent than every 12 weeks, regardless of diagnosis
2. Documentation of positive clinical response to botulinum toxin therapy

## FDA Approved Dose and Indication

| FDA Approved Indication | Botox | Dysport | Myobloc | Xeomin |
|---|---|---|---|---|
| Bladder muscle dysfunction-OAB | X | | | |
| Blepharospasm | X | | | X |
| Cervical Dystonia | X | X | X | X |
| Chronic migraine headache | X | | | |
| Chronic Excessive Salivation | | | X | X |
| Severe hyperhidrosis of axilla | X | | | |
| Incontinence due to detrusor instability associated with neurologic conditions | X | | | |
| Lower limb spasticity | X | X | | |
| Strabismus | X | | | |
| Upper Limb Spasticity | X | X | | X |

- For all indications, dosing requested should be in accordance to FDA-approved dosing and should not exceed the MAXIMUM FDA-approved dosing.
- For NON- FDA approved indications, dosing regimen must be supported by clinical evidence from sources meeting Medicare guidelines.

| Product | FDA Approved Indication and Dosing |
|---|---|
| Botox | **When treating 1 or more indications in adults, the maximum cumulative dose of onabotulinumtoxinA should generally not exceed 400 units in a 3-month interval and in pediatric patients, the total dose should not exceed the lower of 10 units/kg body weight or 340 units, in a 3-month interval**<br>• **Blepharospasm:** Initial, 1.25 to 2.5 units (0.05 to 0.1 mL into each of 3 sites per affected eye MAX, 200 units/30 days cumulative MAX, 200 units/30 days*<br>• **Cervical Dystonia:** Treatment naive: Use lower initial dose. Limit total dose administered into sternocleidomastoid muscles to 100 units or less to decrease dysphagia occurrence. Patients with history of Botox(R) tolerance: 198 to 300 units (mean, 236 units) divided among affected muscles<br>• **Chronic migraine headache:** total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles into each of 31 sites divided across 7 specific head/neck muscle areas (20 units divided in 4 sites in frontalis muscle, 10 units divided in 2 sites in corrugator muscle, 5 units in 1 site in procerus muscle, 30 units divided in 6 sites in occipitalis muscle, 40 units divided in 8 sites in temporalis muscle, 30 units divided in 6 sites in trapezius muscle, and 20 units divided in 4 sites in cervical paraspinal muscle group); doses should be evenly distributed bilaterally in all muscles (except for procerus muscle)*<br>• **Severe hyperhidrosis of axilla:** 50 units (2 mL of a 2.5 units/0.1 mL reconstituted solution) per axilla injected intradermally divided into 0.1 to 0.2 mL aliquots evenly distributed into 10 to 15 sites approximately 1 to 2 cm apart; reinjection may be performed when the benefit of the previous injection lessens<br>• **Overactive Bladde**: total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor<br>• **Incontinence due to detrusor instability associated with neurologic conditions:** 200 units administered as thirty 1-mL (30 mL of a 6.7 units/1 mL reconstituted solution) injections across detrusor muscle. Median time to retreatment is 42 to 48 weeks, but no sooner than 12 weeks; MAX 200 units per treatment*<br>• **Lower limb spasticity:** TOTAL dose of 300 to 400 units IM divided among the following ankle and toe muscles (Start with lowest dose): Gastrocnemius medial head, 75 units divided in 3 sites; gastrocnemius lateral head, 75 units divided in 3 sites; soleus, 75 units divided in 3 sites; tibialis posterior, 75 units divided in 3 sites; flexor hallucis longus, 50 units divided in 2 sites; and flexor digitorum longus, 50 units divided in 2 sites*<br>• **Strabismus:**<br>  • Vertical muscles and horizontal strabismus less than 20 diopters: Initial, 1.25 to 2.5 units injected into any 1 muscle; assess efficacy 7 to 14 days after injection and subsequent doses may be increased up to 2-fold to MAX, 25 units/any muscle as a single injection and 0.15 mL volume per muscle<br>  • Horizontal strabismus between 20 to 50 diopters: Initial, 2.5 to 5 units injected into any 1 muscle; assess efficacy 7 to 14 days after injection and subsequent doses may be increased up to 2-fold to MAX, 25 units/any muscle as a single injection and 0.15 mL volume per muscle<br>  • Persistent sixth nerve palsy for at least 1 month: Initial, 1.25 to 2.5 units injected in the medial rectus muscle; assess efficacy 7 to 14 days after injection and subsequent doses may be increased up to 2-fold to MAX, 25 units/any muscle as a single injection and 0.15 mL volume per muscle |

| | |
|---|---|
| | • **Upper Limb Spasticity:** TOTAL dose up to 400 Units divided among affected muscles.<br>  • Upper limb spasticity, start with lowest dose; usual dosage ranged from 75 to 400 units (using a 5 units/0.1 mL reconstituted solution) per treatment session. Biceps brachii, 60 to 200 units IM divided in 2 to 4 sites; Brachioradialis, 45 to 75 units IM divided in 1 to 2 sites; Brachialis, 30 to 50 units IM divided in 1 to 2 sites; Pronator teres, 15 to 25 units IM in 1 site; Pronator quadratus, 10 to 50 units IM in 1 site; flexor carpi radialis, 12.5 to 50 units IM in 1 site; flexor carpi ulnaris, 12.5 to 50 units IM in 1 site; flexor digitorum profundus, 30 to 50 units IM in 1 site; flexor digitorum sublimis, 30 to 50 units IM in 1 site; Lumbricals/Interossei, 5 to 10 units IM in 1 site; adductor pollicis, 20 units IM in 1 site; flexor pollicis longus, 20 units IM in 1 site; Flexor pollicis brevis/Opponens pollicis 5 to 25 units IM in 1 site; MAX 50 units/site |
| **Dysport** | • **Cervical Dystonia:** Initial, 500 units IM, divided among 2 to 4 affected muscles [3]<br>• Maintenance, 250 units to maximum of 1000 units IM total dose in a single treatment, divided among 2 to 4 affected muscles*<br>• **Lower limb spasticity:** Total doses of 1000 and 1500 units divided among selected muscles at a given treatment session: Flexor digitorum longus, 130 to 200 units IM in 1 to 2 injection sites per muscle; flexor hallucis longus, 70 to 200 units IM in 1 injection site per muscle; gastrocnemius, medial or lateral head, 100 to 150 units IM in 1 injection site per muscle; soleus, 330 to 500 units IM in 3 injection sites per muscle; tibialis posterior, 200 to 300 units IM in 2 injection sites per muscle; no more than 1 mL should be injected into any single injection site; MAX dose for upper and lower limb combined is 1500 units*<br>• **Upper Limb Spasticity:** Total doses of 500 and 1000 units divided among selected muscles at a given treatment sessions: flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum superficialis, brachioradialis, 100 to 200 units IM in 1 to 2 injection sites per muscle; brachialis, biceps brachii, 200 to 400 units IM in 1 to 2 injection sites per muscle; pronator teres, 100 to 200 units IM in 1 injection site; no more than 1 mL should be injected into any single injection site; MAX dose for upper and lower limb combined is 1500 units* |
| **Myobloc** | • **Cervical Dystonia:** Initial, 2500 to 5000 units divided among affected muscles for patients with history of tolerating botulinum toxin injections; use a lower initial dosage for patients without a history of tolerating botulinum toxin injections. Duration of response was 12 to 16 weeks at doses of 5000 or 10,000 units.<br>• **Chronic Excessive Salivation:** Initial, 1500 to 3500 units divided among the parotid and submandibular glands as 500 to 1500 units into each parotid gland and 250 units into each submandibular gland.* |
| **Xeomin** | • **Blepharospasm:** Initial, 50 units (25 units per eye) Max dosage: 100 units per treatment session (50 units per eye)<br>• **Cervical Dystonia:** Initial total dose, 120 units divided<br>• **Chronic sialorrhea:** TOTAL dose of 100 units via intra-salivary gland injection close to the center of the gland, divided as 30 units per side in parotid glands (60 units total) and 20 units per side in submandibular glands (40 units total)** repeat no sooner than every 16 weeks**<br>• **Upper Limb Spasticity:**<br>  • (Clenched fist, flexor digitorum superficialis or flexor digitorum profundus) 25 to 100 units IM in 2 injection sites per muscle; MAX 400 units/treatment session* |

| | |
|---|---|
| | • (Flexed wrist, flexor carpi radialis) 25 to 100 units IM in 1 to 2 injection sites per muscle; MAX 400 units/treatment session*<br>• (Flexed wrist, flexor carpi ulnaris) 20 to 100 units IM in 1 to 2 injection sites per muscle; MAX 400 units/treatment session*<br>• (Flexed elbow, biceps) 50 to 200 units IM in 1 to 4 injection sites per muscle; MAX 400 units/treatment session*<br>• (Flexed elbow, brachialis) 25 to 100 units IM in 1 to 2 injection sites per muscle; MAX 400 units/treatment session*<br>• (Flexed elbow, brachioradialis) 25 to 100 units IM in 1 to 3 injection sites per muscle; MAX 400 units/treatment session*<br>• (Pronated forearm, pronator quadratus) (Thumb-in-palm, flexor pollicis longus) 10 to 50 units IM in 1 injection site per muscle; MAX 400 units/treatment session*<br>• (Pronated forearm, pronator teres) 25 to 75 units IM in 1 to 2 injection sites per muscle; MAX 400 units/treatment session*<br>• (Thumb-in-palm, adductor pollicis, flexor pollicis brevis, or opponens pollicis) 5 to 30 units IM in 1 injection site per muscle; MAX 400 units/treatment session*<br>• (Thumb-in-palm, flexor pollicis longus) 10 to 50 units IM in 1 injection site per muscle; MAX 400 units/treatment session* |

***Repeat no frequently than every 12 weeks**
****Repeat no frequently than every 16 weeks**

## General Background

Botulinum toxin is produced by the gram positive anaerobic bacterium, Clostridium Botulinum. Botulinum toxins interfere with neural transmission by inhibiting the release of acetylcholine which is an important neurotransmitter at the neuromuscular junction. This inhibition results in muscle paralysis. The clinical indications for botulinum toxins have expanded rapidly over the years. They have been found to be useful in treating various conditions such as overactive skeletal muscles (e.g. hemifacial spasm, dystonia, and spasticity), smooth muscles disorders (e.g. detrusor overactivity and achalasia), disorder of the glands (e.g. sialorrhoea and hyperhidrosis) focal muscle spastic disorders and excessive muscle contractions, such as dystonias, spasms, and twitches.

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.

There are currently four botulinum toxin products commercially available in the United States: Botox® (onabotulinumtoxinA), Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), and Xeomin® (incobotulinumtoxinA). Each preparation has distinct pharmacological and clinical profiles, and thus is not interchangeable. Recent changes made to the drug names by the FDA were intended to re-enforce the differences among the botulinum toxins products to prevent medication errors.

There are no NCDs relevant to the botulinum toxin products at the time of this policy revision.

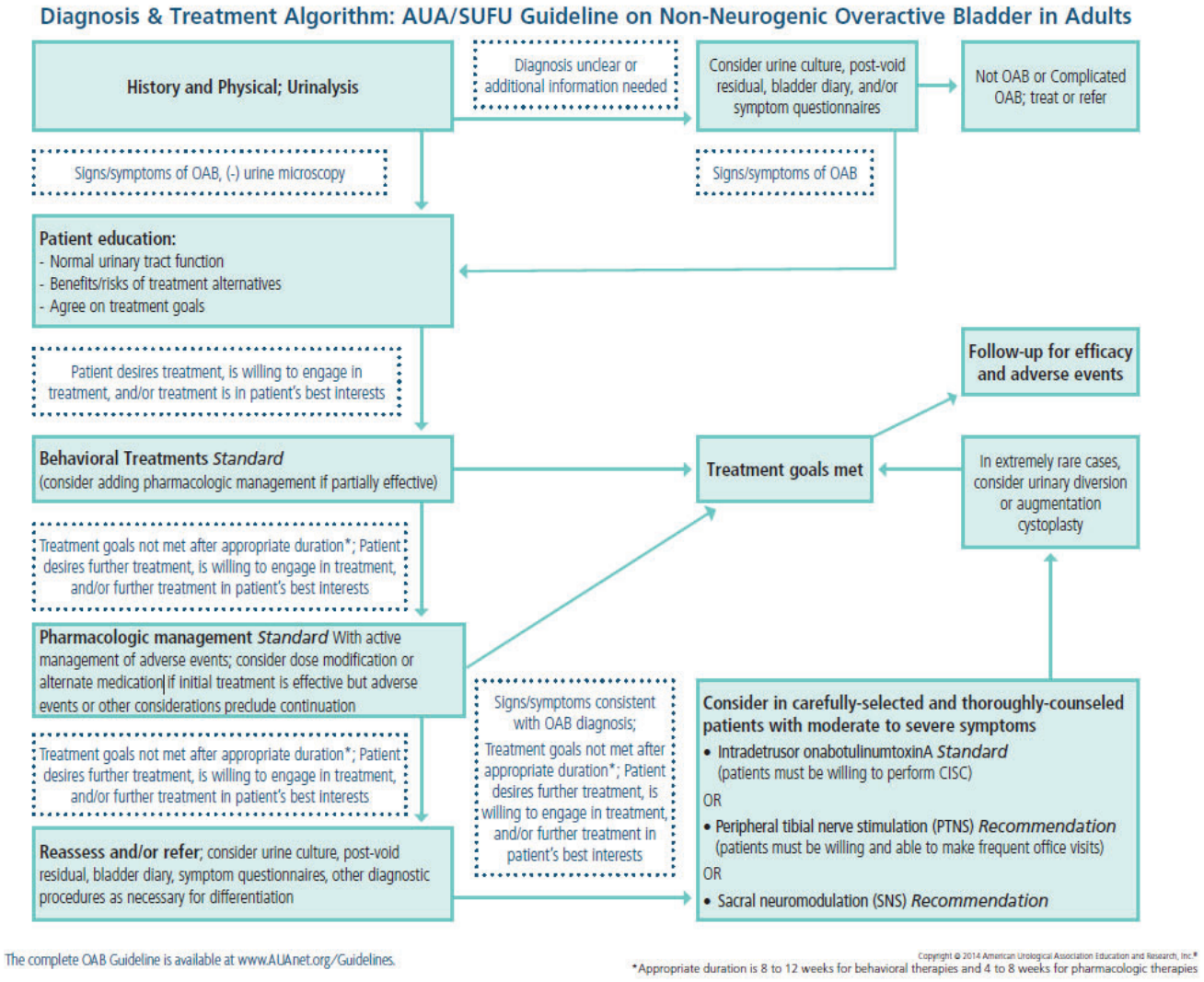
## Precautions and Warnings

A **Black Box Warning** is on all the product labeling for botulinum toxin products:

The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. 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, particularly in those patients who have an underlying condition that would predispose them to these symptoms.

## Clinical Evidence

### A. Overactive Bladder




### B. Achalasia:

Achalasia is a primary motor disorder of the esophagus characterized by insufficient lower esophageal sphincter relaxation and loss of esophageal peristalsis. This results in patients' complaints of dysphagia to solids and liquids, regurgitation, and occasional chest pain with or without weight loss. Endoscopic finding of retained saliva with puckered gastroesophageal junction or barium swallow showing dilated esophagus with birds beaking in a symptomatic patient should prompt appropriate diagnostic and therapeutic strategies.

The main appeal of botulinum toxin treatment is the user-friendly approach that is not much more complicated than performing elective endoscopy and the low rates of serious complications. The standard approach is to place 100 units of the toxin using a scleroneedle just above the squamocolumnar junction in at least 4 quadrants. The toxin is usually diluted in preservative-free saline an injected in 0.5 – 1 ml aliquots. Doses higher than 100 units have not been shown to be more effective and the 12-month success rate ranges from 35 to 41 % . Although the initial (one-month) response rate is high ( > 75%), the therapeutic effect eventually wears off and repeat injection is often required in a significant portion of

the patients. Approximately 50 % of patients relapse and require repeat treatments at 6 – 24-month intervals.9

Oral pharmacologic therapies, such as calcium channel blockers and long-acting nitrates are commonly reserved for patients with achalasia who cannot or refuse to undergo more definitive therapies (PD or surgical myotomy) and those who have failed botulinum toxin injections

**C. Chronic Anal Fissures:**

The aim of the study was to evaluate the efficacy of botulinum toxin injection in the treatment of recurrent anal fissure following lateral internal sphincterotomy. Eighty patients were treated with botulinum toxin (30 units Botox® or 90 units Dysport®), injected into two sites of the internal sphincter. Clinical and manometric results were recorded before and after treatment. If symptoms persisted at 2 months, the examiners could decide to re-treat the patient. The same preparation of serotype A of botulinum neurotoxin was used for reinjection. One month after injection there was complete healing in 54 patients (68 per cent). Eight patients (10 per cent) reported mild incontinence of flatus that had disappeared spontaneously within 2 months. At 2 months, 59 patients (74 per cent) had a healing scar. After reinjection, 11 of 21 re-treated patients reported mild incontinence to flatus that lasted for a few weeks and resolved spontaneously. Anorectal manometry at 1 month demonstrated a significant reduction in both resting anal pressure and maximum voluntary squeeze pressure ($P < 0{\cdot}001$). There were no relapses during a mean value of 57·9 months of follow-up. Botulinum toxin is efficacious in patients with recurrent anal fissure following lateral internal sphincterotomy

**D. Blepharospasm, cervical dystonia, adult spasticity, and headache:**

Table 2 Evidence-based conclusions and recommendations for the efficacy of various botulinum neurotoxin formulations by indication

| Indication | Level A[a] effective | Level B[b] probably effective | Level C[c] possibly effective | Level U[d] insufficient evidence | Level A[e] ineffective | Level B[f] ineffective |
|---|---|---|---|---|---|---|
| Blepharospasm | | OnabotulinumtoxinA, incobotulinumtoxinA | AbobotulinumtoxinA | RimabotulinumtoxinB | | |
| Cervical dystonia | AbobotulinumtoxinA, rimabotulinumtoxinB | OnabotulinumtoxinA, incobotulinumtoxinA | | | | |
| Upper limb spasticity[g] | AbobotulinumtoxinA, onabotulinumtoxinA,[h] incobotulinumtoxinA | RimabotulinumtoxinB | | | | |
| Lower limb spasticity | OnabotulinumtoxinA, abobotulinumtoxinA | | | IncobotulinumtoxinA, rimabotulinumtoxinB | | |
| Chronic migraine | OnabotulinumtoxinA[i] | | | | | |
| Episodic migraine | | | | | OnabotulinumtoxinA | |
| Tension-type headache | | | | | | OnabotulinumtoxinA |

Abbreviations: aboBoNT-A = abobotulinumtoxinA; incoBoNT-A = incobotulinumtoxinA; onaBoNT-A = onabotulinumtoxinA; rimaBoNT-B = rimabotulinumtoxinB.

[a] Level A recommendation for effectiveness signifies intervention should be offered.

[b] Level B recommendation for effectiveness signifies intervention should be considered.

[c] Level C recommendation for effectiveness signifies intervention may be considered.

[d] Level U recommendation signifies insufficient evidence to support or refute effectiveness of intervention.

[e] Level A recommendation for ineffectiveness signifies intervention should not be offered.

[f] Level B recommendation for ineffectiveness signifies intervention should not be considered.

[g] Evidence demonstrates efficacy in reducing spasticity but is inadequate to determine improvement in active function associated with limb spasticity.

[h] Probably superior to tizanidine and exercise alone for reducing spasticity.

[i] Established as effective for decreasing the number and severity of headaches; probably effective in improvement of health-related quality of life.

**E. Chronic Migraine Headache:**

First-line prophylactic medications for chronic migraine include: Propranolol, Amitriptyline, Topiramate, Valproic acid and its derivatives for men (and for women who do not have childbearing potential)

We suggest that treatment for patients with chronic migraine begin with trials of one of these agents.

It is expected that up to 50 percent of patients treated with one of these medications will have at least a 50 percent reduction in the frequency of headaches after three months of treatment, given adequate doses. However, side effects are common and may limit the use of these prophylactic agents.

Second- and third-line agents — For patients with chronic migraine that is refractory to adequate trials of first-line agents, a number of other drugs are potential alternatives, including the following:

Botulinum toxin type A (onabotulinumtoxinA), Erenumab-aooe, Verapamil, Other beta blockers (atenolol, nadolol, metoprolol, timolol), Gabapentin, Magnesium, Riboflavin, Candesartan, Other tricyclic antidepressants (nortriptyline, protriptyline)

**F. Hypersecretory disorders:**

Primary focal hyperhidrosis is a chronic idiopathic disorder of excessive sweating which most often affects the axillae, palms, soles, and forehead. Treatment options include topical or systemic pharmacologic therapy, iontophoresis, or surgical procedures. Drooling may be a disabling problem in parkinsonian syndromes, amyotrophic lateral sclerosis, and cerebral palsy. In these disorders, drooling is primarily due to decreased swallowing rather than increased salivary production and may be amenable to pharmacologic treatment or local radiation and surgery in severe cases.

**G. Axillary hyperhidrosis:**

Two Class I studies and several Class II studies were identified in axillary hyperhidrosis (table e-1 on the Neurology® Web site at www.neurology.org). In a randomized, placebo-controlled, double-blind study of 320 subjects with axillary hyperhidrosis, 242 patients received BoNT and 78 received saline placebo intradermally.3 Patients receiving BoNT had a higher response rate (more than 50% reduction of sweat production compared to baseline sweating) at all time points than those receiving placebo (82% to 95% vs 20% to 37%; $p < 0.001$). There was a similar pattern in the decrease of sweat production, and improvement in quality of life. Treatment-related adverse events were reported by 27 patients (11%) receiving BoNT and 4 (5%) receiving placebo, but this difference was not significant ($p = 0.13$). The mean duration of therapeutic effect was 31 weeks.

In another Class I study of 145 patients with axillary hyperhidrosis, BoNT was injected into one axilla and placebo was injected into the other in a randomized, double-blind manner. At week 2, sweat production was reduced in the axilla that had received BoNT as compared with the placebo-injected side ($p < 0.001$). Injections were well tolerated.

**H. Palmar hyperhidrosis:**

Two Class II and several Class III studies were identified in the use of BoNT in palmar hyperhidrosis. In one randomized, placebo-controlled, double-blind Class II study in 19 patients with palmar hyperhidrosis, sweating was significantly reduced by BoNT as compared with placebo based on gravimetric measurements. There was no resulting muscle weakness. Another Class II study in 11 patients with palmar hyperhidrosis also showed reduction of palmar sweating compared with placebo ($p < 0.001$) using a digitized ninhydrin test. One Class III study evaluated the effect of BoNT on hand muscle strength. No grip weakness resulted in any patients, whereas pinch strength was reduced 2 weeks after the injection. Pinch strength returned to baseline levels 2 months after treatment.

**I. Gustatory sweating:**

Five Class III studies were identified on the use of BoNT in gustatory sweating after parotidectomy. Intradermal injections of BoNT resulted in a significant and consistent reduction of the area of sweating without significant side effects.

**J. Drooling in neurodegenerative diseases and hyperlacrimation:**

Four Class II studies were identified in the treatment of sialorrhea in Parkinson's disease (3 BoNT-A and 1 BoNT-B). One of the studies also included 12 patients with ALS. BoNT significantly reduced the amount of saliva production after injection of the parotid/submandibular glands. Adverse events were reported as mild. Only Class IV studies were identified in the use of BoNT in hyperlacrimation. These consistently showed a reduction of tearing after injections of BoNT into the lacrimal glands.

**K. Detrusor Overactivity:**

Patients who completed a 52-week, phase III trial of onabotulinumtoxinA for NDO were eligible to enter a 3-year, multicenter, open-label extension study of intradetrusor onabotulinumtoxinA (200U or 300U). Patients were treated "as needed" based on their request and fulfillment of prespecified qualification criteria (≥12 weeks since previous treatment and a UI episode threshold). Assessments included change from study baseline in UI episodes/day (primary efficacy measure), volume/void, and Incontinence Quality of Life (I-QOL) total score (week 6); duration of effect; adverse events (AEs); and initiation of de novo clean intermittent catheterization (CIC). Data are presented for up to six treatments.

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.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.

The best studied for the treatment of urinary incontinence as a result of neurogenic detrusor overactivity and overactive bladder/idiopathic detrusor overactivity is onabotulinum toxin A. This brand is only approved for the treatment of urinary incontinence as a result of neurogenic detrusor overactivity at a dose of 200 U and idiopathic detrusor overactivity at a dose of 100 U. In patients with detrusor overactivity as a result of spinal cord injury or multiple sclerosis, 200 U of onabotulinum toxin A should be injected in 30 different sites above the trigone. It was shown to be highly effective in curing or decreasing urinary symptoms of incontinence, increasing quality of life, increasing bladder capacity and decreasing maximal detrusor pressure. This effect was independent of the concomitant use of oral anticholinergic drugs. Adverse events were mild, mainly urinary tract infections and high post-void residual requiring clean intermittent catheterization. In patients with overactive bladder/idiopathic detrusor overactivity, 100 U of onabotulinum toxin A should be injected in 20 sites above the trigone. It markedly decreases urinary incontinence and improves quality of life. Frequency and urgency episodes are also decreased. Adverse events are mild, mainly urinary tract infections and urinary retention. The latter occurred in just 5% of the patients. Candidates for onabotulinum toxin A treatment should be warned that the effect of the toxin is transient and that repeated injections will be required to maintain the effect in the long term. There is no evidence that repeated injections will have a decreased efficacy.

These studies were the final step of intense clinical research that started in 2000, when onabotA injections in the bladder of SCI patients were first suggested as an alternative treatment to NDO refractory to antimuscarinic drugs. Pivotal studies of onabotA in idiopathic detrusor overactivity have concluded with very positive preliminary reports (Nitti et al. Late Breaking News, AUA annual meeting 2012, and Chapple et al., non-discussed poster, ICS, 2012). FDA approved onabotA 100 U for the treatment of urinary incontinence as a result of OAB/IDO in January 2013.

## HCPCS Code, Dosage Form & Route of Administration

| HCPCS Code | Description | Dosage Form | Route of Administration |
|---|---|---|---|
| J0585 | Botox (OnabotulinumtoxinA) | 100 units or 200 units in single dose vial | Intradermal or Intramuscular |
| J0586 | Dysport (AbobotulinumtoxinA) | 500 units or 300 units single dose vial | Intramuscular |
| J0587 | Myobloc (RimabotulinumtoxinB) | 2,500 units/0.5 mL or 5,000 units/mL or 10,000 units/2mL single dose vial | Intraglandular |
| J0588 | Xeomin (IncobotulinumtoxinA) | 50 units, 100 units or 200 units single dose vial | Intramuscular or Intraglandular |

## Acronyms

NCD = National Coverage Determination

LCD = Local Coverage Determination

ADL = Activities of Daily Living

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