OnabotulinumtoxinA (Botox®)

NDC CODE(S) 00023-1145-XX BOTOX 100UNIT Solution Reconstituted (ALLERGAN)
00023-3919- XX BOTOX COSMETIC 50UNIT Solution Reconstituted (ALLERGAN/BOTOX)
00023-3921- XX BOTOX 200UNIT Solution Reconstituted (ALLERGAN)
00023-9232- XX BOTOX COSMETIC 100UNIT Solution Reconstituted (ALLERGAN/BOTOX)

DESCRIPTION

Botulinum toxin, produced by the bacterium *Clostridium botulinum*, is one of the most potent naturally occurring neurotoxins known. It induces chemodenervation by first binding to acceptors on motor nerve terminals. It then enters the terminals and blocks the release of acetylcholine and other neurotransmitters at the neuromuscular junction. This renders smooth and striated muscles incapable of contraction. Acetylcholine also mediates the sympathetic innervation of the sweat glands, explaining how botulinum toxin disrupts the cholinergic outflow to the skin and halts glandular secretion.

The minute amount of toxin used clinically produces only partial, localized chemical denervation with transient results. Over time, axons generate temporary sprouts which release acetylcholine and the original nerve terminal is eventually re-established, ending the toxin's therapeutic activity.

Seven antigenic-specific serotypes of botulinum toxin have been identified, types A, B, C-1, D, E, F and G, but only botulinum toxin types A and B are commercially available. These commercial preparations of the two serotypes (three of serotype A and one of serotype B) vary widely in potency and dosage. They have been given different names to reinforce these differences and to prevent medication errors. It is emphasized that the use and dosage of different formulations of botulinum toxin is not interchangeable.

This policy addresses only onabotulinumtoxinA, commercially available as Botox®.

POLICY

- OnabotulinumtoxinA for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Achalasia - esophageal
  - Blepharospasm
  - Cerebral palsy with concurrent equinus gait
  - Cerebral palsy-related spasticity, localized or segmental
  - Cervical dystonia
  - Chronic anal fissure
  - Diplegia
  - Focal upper limb dystonia (e.g., organic writer's cramp)
  - Hemifacial spasms
  - Hemiplegia, spastic
  - Hereditary spastic paraplegia
  - Hyperhidrosis
  - Laryngeal dystonia (Spasmodic dysphonia)
  - Lower limb spasticity
  - Monoplegia
  - Oromandibular dystonia (orofacial dyskinesia)
  - Other paralytic syndromes
  - Overactive Bladder (OAB)

  - Paraplegia
  - Quadriplegia
  - Schilder's disease
  - Spasticity due to multiple sclerosis
  - Sialorrhea
  - Spastic hemiplegia
  - Strabismus
  - Upper limb spasticity
  - Urinary incontinence
  - Ventral Hernia
- OnabotulinumtoxinA for the Prophylaxis of Chronic Migraine Headache is considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**
- OnabotulinumtoxinA for the treatment or prevention of **ANY OTHER** disease or conditions is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

- Patient is at least 18 years of age (unless otherwise specified); **AND**

Universal Criteria

- Patient evaluated for any disorders which may contribute to respiratory or swallowing difficulty; **AND**
- Patient does not have a hypersensitivity to any botulinum toxin product; **AND**
- Patient does not have an active infection at the proposed injection site; **AND**
- Patient is not on concurrent treatment with another botulinum toxin (i.e., abobotulinumtoxinA, incobotulinumtoxinA, rimabotulinumtoxinB, etc.) **AND**

Blepharospasms

- Patient is at least 12 years of age

Cervical Dystonia

- Patient is at least aged 16 years of ager greater; **AND**
- Patient has a history of recurrent involuntary contraction of one or more muscles in the neck; **AND**
  - Patient has sustained head tilt; **OR**
  - Patient has abnormal posturing with limited range of motion in the neck

Strabismus

- Patient is at least aged 12 years of ager greater

Spastic Conditions

- Patient has one of the following:
  - Upper/Lower Limb spasticity in adults (i.e., used post-stroke for spasms)
  - Pediatric upper limb spasticity in patients aged 2 years or greater (i.e., used post-stroke for spasms or for spasms related to cerebral palsy)

- Pediatric lower limb spasticity in patients aged 2 years or greater
- Spasticity due to multiple sclerosis or Schilder's disease
- Acquired spasticity secondary to spinal cord or brain injuries
- Spastic Plegic conditions including Monoplegia, Diplegia, Hemiplegia, Paraplegia (including Hereditary spastic paraplegia) and Quadriplegia
- Hemifacial Spasm

Severe Primary Axillary Hyperhidrosis

- Patient has tried and failed ≥ 1 month trial of a topical agent (e.g., aluminum chloride, glycopyrronium, etc.); **AND**
  - Patient has a history of medical complications such as skin infections or significant functional impairments; **OR**
  - Patient has had a significant burden of disease or impact to activities of daily living due to condition (e.g., impairment in work performance/productivity, frequent change of clothing, difficulty in relationships and/or social gatherings, etc.)

Prophylaxis for Chronic Migraines

- Not used in combination with prophylactic calcitonin gene-related peptide (CGRP) inhibitors (e.g., eptinezumab, erenumab, galcanezumab, fremanezumab, etc.) *(NOTE: This does not include CGRP inhibitors used for acute treatment [i.e., ubrogepant])*; **AND**
- Patient is utilizing prophylactic intervention modalities (i.e., pharmacotherapy, behavioral therapy, physical therapy, etc.); **AND**
- Patient has 15 or more headache (tension-type-like and/or migraine-like) days per month for at least 3 months; **AND**
  - Patient has had at least five attacks with features consistent with migraine (with and/or without aura)**§**; **AND**
  - On at least 8 days per month for at least 3 months:
    - Headaches have characteristics and symptoms consistent with migraine**§**; **OR**
    - Patient suspected migraines are relieved by a triptan or ergot derivative medication; **AND**
- Patient has failed at least an 8-week trial of any two oral medications for the prevention of migraines (see list of migraine-prophylactic medications below for examples)

Esophageal Achalasia

- Patient is at high risk of complication from pneumatic dilation, ~~or~~ surgical myotomy or perioral endoscopic myotomy (POEM); **OR**
- Patient has had treatment failure with pneumatic dilation, ~~or~~ surgical myotomy or POEM; **OR**
- Patient has had perforation from pneumatic dilation; **OR**
- Patient has an epiphrenic diverticulum or hiatal hernia; **OR**
- Patient has esophageal varices

Focal Dystonias

- Focal upper limb dystonia
  - Patient has functional impairment; **OR**
  - Patient has pain as a result
- Laryngeal dystonia
- Oromandibular dystonia
  - Patient has functional impairment; **OR**

- Patient has pain as a result

Incontinence due to detrusor overactivity

- Patient is at least 5 years of age; **AND**
- Patient does not have a current, untreated urinary tract infection; **AND**
- Patient has detrusor overactivity associated with a neurologic condition (i.e., spinal cord injury, multiple sclerosis, etc.) that is confirmed by urodynamic testing; **AND**
- Patient has failed a 1 month or longer trial of **two** medications from either the antimuscarinic (i.e., darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or trospium) or beta-adrenergic (i.e., mirabegron) classes

Overactive Bladder (OAB)

- Patient does not have a current, untreated urinary tract infection; AND
- Patient has symptoms of urge urinary incontinence, urgency, and frequency; AND
- Patient has failed a 1 month or longer trial of two medications from either the
- antimuscarinic (i.e., darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine or
- trospium) and/or beta-adrenergic (i.e., mirabegron) classes

Severe Palmar Hyperhidrosis

- Patient has tried and failed ≥ 1 month trial of a topical agent (e.g., aluminum chloride, etc.); **AND**
- Patient has failed with iontophoresis; **AND**
  - Patient has a history of medical complications such as skin infections or significant functional impairments; **OR**
  - Patient has had a significant impact to activities of daily living due to condition

Chronic Anal Fissure

- Other causes of disease have been ruled out (i.e., Crohn's Disease, etc.); **AND**
- Patient has failed on non-pharmacologic supportive measures (i.e., sitz baths, psyllium fiber, bulking agents, etc.); **AND**
- Patient has tried and failed a ≥ 1 month trial of conventional pharmacologic therapy (e.g. oral/topical nifedipine, diltiazem, and/or topical nitroglycerin, bethanechol, etc.)

Ventral Hernia

- Patient has a large ventral hernia with loss of domain or contaminated ventral hernia; **AND**

Used preoperatively in patients scheduled to receive abdominal wall reconstruction (AWR)

Migraine-Prophylaxis Oral Medications *(list not all-inclusive)*
• Antidepressants (e.g., amitriptyline, fluoxetine, nortriptyline, etc.) • Beta blockers (e.g., propranolol, metoprolol, nadolol, timolol, atenolol, pindolol etc.) • Angiotensin converting enzyme inhibitors/angiotensin II receptor blockers (ex. lisinopril, candesartan, etc.) • Anti-epileptics (e.g., divalproex, valproate, topiramate, etc.) • Calcium channels blockers (e.g., verapamil, etc.)

Migraine without aura
• At least five attacks have the following:
  ○ Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
  ○ Headache has at least two of the following characteristics:
  – Unilateral location
  – Pulsating quality
  – Moderate or severe pain intensity
  – Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs); **AND**
  ○ During headache at least one of the following:
  – Nausea and/or vomiting
  – Photophobia and phonophobia

Migraine with aura
• At least two attacks have the following:
  ○ One or more of the following fully reversible aura symptoms:
  – Visual
  – Sensory
  – Speech and/or language
  – Motor
  – Brainstem
  – Retinal; **AND**
  ○ At least three of the following characteristics:
  – At least one aura symptom spreads gradually over ≥5 minutes~~, and/or t~~
  – Two or more symptoms occur in succession
  – Each individual aura symptom lasts 5 to 60 minutes
  – At least one aura symptom is unilateral
  – At least one aura symptom is positive (e.g., scintillations and pins and needles)
  – The aura is accompanied, or followed within 60 minutes, by headache

RENEWAL CRITERIA

- Patient continues to meet universal and indication specific criteria as identified in Initial Approval Criteria; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: symptoms of a toxin spread effect (e.g., asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, swallowing/breathing difficulties, etc.), severe hypersensitivity reactions, severe pulmonary effects (e.g., reduced pulmonary function), corneal exposure/ulceration, retrobulbar hemorrhage, bronchitis/upper-respiratory tract infections, autonomic dysreflexia, urinary tract infection, and urinary retention, etc.; **AND**
- Disease response as evidenced by the following:

Blepharospasms

- Improvement of severity and/or frequency of eyelid spasms

Cervical dystonia

- Improvement in the severity and frequency of pain; **AND**
- Improvement of abnormal head positioning

Strabismus

- Improvement in alignment of prism diopters compared to pre-treatment baseline

Focal Upper/Lower Limb Spasticity

- Decrease in tone and/or resistance, of affected areas, based on a validated measuring tool (e.g., Ashworth Scale, Physician Global Assessment, Clinical Global Impression (CGI), etc.)

Hemifacial Spasms

- Decrease in frequency and/or severity of spasm, or a decrease in tone and/or improvement in asymmetry to the affected side of the face

Severe primary axillary hyperhidrosis

- Significant reduction in spontaneous axillary sweat production; **AND**
- Patient has a significant improvement in activities of daily living

Prophylaxis for chronic migraines

- Significant decrease in the number, frequency, and/or intensity of headaches; AND
- Improvement in function; AND
- Patient continues to utilize prophylactic intervention modalities (i.e., pharmacotherapy, behavioral therapy, physical therapy, etc.)

Esophageal achalasia

- Improvement and/or relief in symptoms (e.g., dysphagia, pain, etc.); **OR**
- Improvement in esophageal emptying as evidenced by functional testing

Focal Dystonias

- **Focal upper limb dystonia**
  - Improvement in pain and/or function
- **Laryngeal dystonia**
  - Improvement in voice function or quality
- **Oromandibular dystonia**
  - Improvement in pain and function

Sialorrhea associated with neurological disorders

- Significant decrease in saliva production

Incontinence due to detrusor overactivity

- Patient does not have a current, untreated urinary tract infection; **AND**
- Significant improvements in weekly frequency of incontinence episodes; **AND**
- Patient's post-void residual (PVR) periodically assessed as medically appropriate

Overactive bladder (OAB)

- Patient does not have a current, untreated urinary tract infection; **AND**
- Significant improvement in daily frequency of urinary incontinence or micturition episodes and/or volume voided per micturition; **AND**
- Patient's post-void residual (PVR) periodically assessed as medically appropriate

Severe Palmar Hyperhidrosis

- Significant reduction in spontaneous palmar sweat production; **AND**
- Patient has a significant improvement in activities of daily living

Chronic anal fissure

- Complete healing of anal fissure; **OR**
- Symptomatic improvement of persistent fissures

Spastic Conditions, Other (Plegias, etc.)

- Decrease in tone and/or resistance, of affected areas, based on a validated measuring tool (e.g., Ashworth Scale, Physician Global Assessment, Clinical Global Impression (CGI), etc.)

Ventral Hernia

- May not be renewed

DOSAGE/ADMINISTRATION

Indication	Dose
Blepharospasm	1.25-2.5 Units (0.05—0.1 ml per site) injected into each of 3 sites per affected eye every three months. There appears to be little benefit obtainable from injecting more than 5 Units per site. The effect of treatment lasts an average of 12 weeks. Cumulative dose in 30 days should not exceed 200 units
Cervical Dystonia	198 Units to 300 Units divided among the affected muscles. No more than 50 Units per site. May re-treat in 12 weeks.
Strabismus	Based on muscle(s) affected, 1.25-2.5 Units in any one muscle initially. Subsequent doses may be increased up to two-fold compared to previously administered dose. No more than 25 Units in any one muscle for recurrent cases. The effect of treatment usually lasts about 12 weeks.
Esophageal Achalasia	100 Units (20-25 Units per quadrant) per administration, dose may be repeated in 6 months (24 weeks)
Upper Limb Spasticity	Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with Botox. For pediatrics, localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended.

Upper Limb Spasticity (contd.)	Adults • In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles at a given treatment session, no sooner than every 12 weeks. Pediatrics • The recommended dose for treating pediatric upper limb spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles. The total dose of Botox administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower. The maximum cumulative dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval.
Lower Limb Spasticity	Adults • 300 to 400 Units divided among 5 muscle groups (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus), no sooner than every 12 weeks. Pediatrics • The recommended dose for treating pediatric lower limb spasticity is 4 Units/kg to 8 Units/kg divided among the affected muscles. The total dose of Botox administered per treatment session in the lower limb should not exceed 8 Units/kg or 300 Units, whichever is lower. The maximum cumulative dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval.
Chronic Migraine	155 Units administered intramuscularly (IM) as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas. The recommended re-treatment schedule is every 12 weeks.
Severe Primary Axillary Hyperhidrosis	50 Units intradermally per axilla every 16 weeks
Sialorrhea	15-40 Units in the parotid gland injected in two places and 10-15 Units in the submandibular glands (total dose from 50-100 Units per patient/administration), repeated in 3 months (12 weeks), if needed.
Neurogenic Bladder/Detrusor Overactivity	Adults • 200 Units per treatment injected into the detrusor muscle using 30 injections (6.7 units each). Pediatrics • Weight ≥ 34 kg: 200 Units per treatment injected into the detrusor muscle using 20 injections. • Weight < 34 kg: 6 Units/kg per treatment injected into the detrusor muscle using 20 injections. *Note: Re-inject no sooner than 12 weeks from the prior bladder injection.*
Overactive Bladder (OAB)	100 Units per treatment injected into the detrusor muscle using 20 injections (5 units each). Re-inject no sooner than 12 weeks from the prior bladder injection.
Palmar Hyperhidrosis	50-100 units per hand, repeated every 6 months (24 weeks), as needed

Hemifacial Spasms	Recommended dose of 20 to 40 U, divided among affected muscles. Retreatment within 12 weeks
Oromandibular Dystonia	80 units per side (~40 units injected into both the masseter and submentalis complex muscles) every 12 weeks.
Laryngeal Dystonia	Starting dose of 1.25-5 units into thyroarytenoid muscle. Dose is titrated based on response and side effects after. Retreat every 3 months (12 weeks).
Chronic Anal Fissures	Recommended doses of up to 25 units, injected into the anal sphincter. Retreat every 3 months (12 weeks).
Ventral Hernia	500 units divided among abdominal muscles, injected 2-4 weeks prior to AWR surgery. *May not be renewed.*
All other indications (unless otherwise specified)	Not to exceed a cumulative dose of 400 U (for one or more indications) every 12 weeks

- When initiating treatment, the lowest recommended dose should be used.
- In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3-month (12-week) interval (unless used for Ventral Hernia).
- In treating pediatric patients, the total should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month (12-week) interval.
- Unless otherwise stated, re-treatment should occur no sooner than 12 weeks from the prior injection.

LENGTH OF AUTHORIZATION

- Coverage will be provided for six months and may be renewed.
- Preoperative use in Ventral Hernia may **NOT** be renewed

DOSING LIMITS

Max Units (per dose and over time) [HCPCS Unit]:

Indication	Billable Units	Per # days
Blepharospasm	**200**	**84**
Cervical Dystonia	**300**	**84**
Strabismus	**100**	**84**
Esophageal Achalasia	**100**	**168**
Adult Upper Limb Spasticity	**400**	**84**
Adult Lower Limb Spasticity	**400**	**84**
Chronic Migraine	**200**	**84**
Severe Primary Axillary Hyperhidrosis	**100**	**112**
Sialorrhea	**100**	**84**
Neurogenic Bladder/Detrusor Overactivity	**200**	**84**
Overactive Bladder	**100**	**84**

Chronic Anal Fissures	**100**	**84**
Palmar Hyperhidrosis	**200**	**168**
Pediatric Upper Limb Spasticity	**300**	**84**
Pediatric Lower Limb Spasticity	**300**	**84**
Laryngeal Dystonia	**100**	**84**
Hemifacial Spasms	**100**	**84**
Oromandibular Dystonia	**200**	**84**
Ventral Hernia	**500**	**N/A**
All other indications	**400**	**84**

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

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