Clinical Policy Title:	onabotulinumtoxinA
Policy Number:	RxA.591
Drug(s) Applied:	Botox®
Original Policy Date:	03/06/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

OnabotulinumtoxinA (Botox®) is an acetylcholine release inhibitor and a neuromuscular blocking agent.
It is indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.
- 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.
- Prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).
- Treatment of spasticity in patients 2 years of age and older.
- Treatment of cervical dystonia (CD) in adult patients, to reduce the severity of abnormal head position and neck pain.
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia in patients ≥ 12 years of age.
- Treatment of strabismus in patients ≥ 12 years of age.
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

Limitation(s) of use:
Safety and effectiveness of Botox® have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month)
- Treatment of hyperhidrosis in body areas other than axillary

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
onabotulinumtoxinA (Botox®)	Blepharospasm	Average Duration of Effect:12.5 weeks Initial Dose (Botox naïve): 1.25 to 2.5 units into each of 3 sites per affected eye; total 15 units per treatment session Subsequent Dose (Botox experienced): 5 units per site, 15 units per eye and 30 units per treatment	See dosing regimen
	Strabismus	Average Duration of Effect: 6-8 weeks to 6-12 months	See dosing

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		Initial Dose (Botox naïve): - Vertical muscles, or horizontal strabismus < 20 prism diopters: Up to 2.5 Units per muscle and 5 Units per treatment - Horizontal strabismus 20 to 50 prism diopters: Up to 5 Units per site and 10 Units per treatment - VI nerve palsy: 2.5 Units in the medical rectus muscle and 2.5 Units per treatment Subsequent Doses (Botox experienced): - Vertical and horizontal strabismus: Up to the lower of a two-fold increase or 25 Units per site and 50 Units per treatment - VI nerve palsy: Up to the lower of a two-fold increase or 25 Units IM per muscle and 25 Units per treatment	regimen
	Cervical dystonia	Average Duration of Effect: 4 weeks to 3 months Average Dose: 198 to 300 units (mean, 236 units) divided among affected muscles	300 units every 12 weeks
	Oromandibular dystonia (OMD), upper extremity dystonia, upper extremity essential tremor*	Average Duration of Effect: 10 to 14 weeks Average Dose: 25 units per muscle per treatment	10 units/kg body weight or 340 Units for pediatrics, or 400 Units for adults
	Laryngeal dystonia*	Average Dose: 25 units per treatment	25 units every 12 weeks
	Overactive bladder	Average Duration of Effect: 12 weeks Average Dose: Total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor. Repeat doses should be 12 weeks apart	100 units every 12 weeks
	Urinary incontinence associated with neurologic condition	Average Duration of Effect: 12 weeks Average Dose: total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor. Repeat doses should be 12 weeks apart	200 units every 12 weeks
	Spastic muscle contracture of pediatric cerebral palsy*	Average Duration of Effect: 1-6 months Average Dose: 3 to 6 units/kg (maximum 12 units/kg). Total dose 82 to 220 units divided among affected muscles	See dosing regimen
	Childhood myoclonus following failure of	Average Duration of Effect: 4-8 months Average Dose: 8 to 80 units/kg	See dosing regimen

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
	Baclofen, benzodiazepines, and antiseizure medications*		
	Chronic anal fissure*	Average Duration of Effect: Single Injection Average Dose: 25 units per treatment	25 units every 12 weeks
	Internal anal sphincter achalasia (IAS), HD*	Average Duration of Effect: Single treatment. Patient may require repeat treatment. Average Dose: up to 100 units per treatment	100 units every 12 weeks
	Axillary hyperhidrosis	Average Duration of Effect: 4-12 months Average Dose: 50 units per axilla	100 units every 12 weeks
	Migraines	Average Duration of Effect: 3-4 months Average Dose: 155 units divided across 7 head/neck muscles	155 units every 12 weeks
	Adult upper and lower limb spasticity	Average Duration of Effect: 12 weeks Average Dose: Up to 50 units per injection site and up to 400 units total per treatment	400 units every 12 weeks
	Pediatric upper and lower limb spasticity	Average Duration of Effect: 12 weeks Average Dose for upper limb spasticity: 6 units/kg or 200 units (whichever is lower) per treatment Average Dose for lower limb spasticity: 8 units/kg or 300 units (whichever is lower) per treatment	See dosing regimen
	Neurogenic detrusor overactivity (NDO)	• Adults: 200 Units of Botox® per treatment- (median time to retreatment: 42 to 48 weeks), but no sooner than 12 weeks. • Children and Adolescents 5 to 17 years weighing 34 kg or more: 200 units IM per treatment- (median time to retreatment: 30 weeks), but no sooner than 12 weeks. • Children and Adolescents 5 to 17 years weighing less than 34 kg: 6 Units/kg body weight- (median time to retreatment: 30 weeks), but no sooner than 12 weeks.	Adults: 200 Units, Greater than or equal to 34 kg: 200 Units, Less than 34 kg: 6 Units/kg

Dosage Forms

- Vial of powder for solution for injection: 100 units, 200 units.

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Cervical Dystonia (must meet all):

1. Diagnosis of CD (*see Appendix D*):
2. Prescribed by or in consultation with a neurologist, orthopedist, physiatrist, or physical medicine and rehabilitation specialist;
3. 16 years of age or older;
4. Member is experiencing involuntary contractions of the neck and shoulder muscles (e.g., splenius capitis, sternocleidomastoid, levator scapulae, scalene, trapezius, semispinalis capitis) resulting in abnormal postures or movements of the neck, shoulder or head;
5. Contractions are causing pain and functional impairment;
6. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
7. Dose does not exceed total 100 units in the SCM (sternocleidomastoid) muscle and total 300 units per treatment session;
   (*Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of Botox should be at a lower dose, with subsequent dosing adjusted based on individual response*.)

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

B. Blepharospasm associated with dystonia (must meet all)**:**

1. Diagnosis of blepharospasm (i.e., abnormal contraction of eyelid muscles);
2. Prescribed by or in consultation with a neurologist or ophthalmologist;
3. 12 years of age or older;
4. Member has significant disability in daily functional activities due to interference with vision;
5. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
6. Dose does not exceed 2.5 units into each of 3 sites per affected eye. Cumulative dose of in a 30-day period should not exceed 200 units.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

C. Other Dystonias and Essential Tremor (off-label) (must meet all)**:**

1. Diagnosis of dystonia (including laryngeal dystonia, OMD, upper extremity dystonia) or upper extremity essential tremor (*see definitions and types in Appendices D and E*);
2. Prescribed by or in consultation with a neurologist, orthopedist, physiatrist, or physical medicine and rehabilitation specialist;
3. Failure of a trial of carbidopa/levodopa or trihexyphenidyl unless contraindicated or clinically significant adverse effects are experienced;

4. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. Dose does not exceed 400 units per single treatment with the following exceptions:
   a. Oromandibular dystonia: 25 units per muscle per treatment session;
   b. Laryngeal dystonia (spasmodic dysphonia), upper extremity essential tremor: Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use and member age (prescriber must submit supporting evidence);

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

D. Upper and Lower Limb Spasticity (must meet all)**:**

1. Diagnosis of upper or lower limb spasticity (associated with paralysis, multiple sclerosis, stroke, cerebral palsy);
2. Prescribed by or in consultation with a neurologist, orthopedist, physiatrist, or physical medicine and rehabilitation specialist;
3. 2 years of age or older;
4. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. Request meets one of the following (a or b):
   a. If age 18 years of age or older, dose does not exceed 400 units per treatment session;
   b. If age is 2 to 17 years of age, dose does not exceed 6 units/kg or 200 units (whichever is lower) per treatment session for upper limb spasticity.
   c. If age is 2 to 17 years of age, dose does not exceed 8 units/kg or 300 units (whichever is lower) per treatment session for lower limb spasticity.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

E. Chronic Migraine (must meet all)**:**

1. Diagnosis of chronic migraine (15 headache days per month or more, for at least 3 months with headache lasting 4 hours a day or longer);
2. Prescribed by or in consultation with a neurologist, headache specialist or pain specialist;
3. 18 years of age or older;
4. Failure of an 8-week trial of at least 2 of the following oral migraine preventative therapies, from different therapeutic classes: antiepileptic drugs (e.g., divalproex sodium, sodium valproate, topiramate), beta-blockers (e.g., metoprolol, propranolol, timolol), antidepressants (e.g., amitriptyline, venlafaxine), unless contraindicated or clinically significant adverse effects are experienced;
5. Botox® is not prescribed concurrently with injectable CGRP inhibitors (e.g., Aimovig®, Ajovy®, Emgality®);
6. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
7. Dose does not exceed 155 units per treatment session.

Approval duration
Medicaid: 168 days (two 12-week treatment sessions)
Commercial: 6 months

G. Primary Axillary Hyperhidrosis* (must meet all)**:**

1. Diagnosis of severe primary axillary hyperhidrosis (e.g., resulting in medical complications such as skin maceration and infection or significant disruption of professional/social life);
2. Prescribed by or in consultation with a neurologist or dermatologist;
3. 18 years of age or older;
4. Failure of a 6-month trial of topical aluminium chloride, unless contraindicated or clinically significant adverse effects are experienced;
5. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
6. Dose does not exceed 50 units per axilla per treatment session.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

H. Overactive Bladder and Urinary Incontinence (must meet all)**:**

1. Diagnosis (a or b):
   a. Overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults
   b. Urinary incontinence associated with a neurologic condition (e.g., spinal cord injury, MS);
2. Prescribed by or in consultation with a neurologist or urologist;
3. 18 years of age or older;
4. Failure of a trial of at least two anticholinergic agents and one oral beta-3 agonist medication (e.g., oxybutynin chloride, tolterodine tartrate, mirabegron), each used for at least 30 days, unless contraindicated or clinically significant adverse effects are experienced;
5. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
6. Dose does not exceed (a or b):
   a. Overactive bladder: 100 units per treatment session;
   b. Urinary incontinence: 200 units per treatment session.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

I. Esophageal Achalasia (off-label) (must meet all)**:**

1. Diagnosis of esophageal achalasia (i.e., failure of relaxation of the lower esophageal sphincter accompanied by loss of peristalsis in the distal esophagus);
2. Prescribed by or in consultation with a gastroenterologist;
3. 18 years of age or older;
4. Member is not a good candidate for pneumatic dilation or myotomy (e.g., high surgical risk due to age, comorbidities);
5. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
6. Dose does not exceed 100 units per treatment session.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

J. Hirschsprung's Disease and Internal Anal Sphincter Achalasia (off-label) (must meet all):

1. Diagnosis (a or b):
   a. Hirschsprung's disease (HD) (i.e., heritable motor disorder of the gut with failure of the colon to relax causing functional obstruction; usually diagnosed infancy or childhood) (i or ii):
      i. Botox® will be used for constipation due to increased internal anal sphincter tone after surgery;
      ii. Member is diagnosed with ultra-short segment HD;
   b. Internal anal sphincter (IAS) achalasia (i.e., lack of rectoanal inhibitory reflex on anal manometry; presents in infancy – may mimic HD);
2. Prescribed by or in consultation with a gastroenterologist;
3. Failure of a trial of stool softeners and laxatives, unless clinically adverse effects are experienced or all are contraindicated;
4. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. Dose does not exceed 100 units per treatment session.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

K. Chronic Anal Fissure (off-label) (must meet all)**:**

1. Diagnosis of chronic anal fissures;
2. Prescribed by or in consultation with a gastroenterologist or colorectal surgeon;
3. 18 years of age or older;
4. Failure of a trial of nitroglycerin 0.2% ointment, unless contraindicated or clinically significant side effects are experienced;
5. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
6. Dose does not exceed 25 units per treatment session.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

L. Neurogenic detrusor overactivity

1. Diagnosis of pediatric detrusor overactivity associated with a neurologic condition;
2. Prescribed by or in consultation with a urologist;
3. Age of 5 years and older;
4. Member has had an inadequate response to or is intolerant of anticholinergic medication;
5. Member meets a or b:
   a. Total dose does not exceed 200 units for those greater than or equal to 34 kg body weight;
   b. Total dose does not exceed 6 units/kg for those less than 34 kg body weight;

Approval duration
Medicaid: 3 months
Commercial: 3 months

M. Strabismus (eye misalignment) (must meet all)**:**

1. Member meets one of the following diagnosis (a, b or c):
   a. Vertical strabismus (superior and inferior rectus muscles, superior and inferior oblique muscles);

b. Horizontal strabismus (medical and lateral rectus muscles) (i or ii):
   i. Horizontal strabismus of less than 20 prism diopters;
   ii. Horizontal strabismus of 20 to 50 prism diopters;

c. Persistent sixth (VI) cranial nerve (abducens nerve) palsy of greater than or equal to one month involving the lateral rectus muscle;

2. Prescribed by or in consultation with a neurologist or ophthalmologist;
3. 12 years of age or older;
4. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. Dose requested meets one of the following (a, b or c):
   a. Vertical strabismus, and/or horizontal strabismus of less than 20 prism diopters: Dose does not exceed 2.5 Units per muscle and 5 Units per treatment session;
   b. Horizontal strabismus of 20 to 50 prism diopters: Dose does not exceed 5 Units per muscle and 10 Units per treatment session;
   c. Persistent VI nerve palsy of one month or longer duration: Dose does not exceed 2.5 Units in the medial rectus muscle per treatment session (limited to treatment of one eye).

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

II. Continued Therapy Approval

A. Chronic Migraine (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria for the covered indications and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If member has received 2 or more Botox® treatment sessions, has experienced and maintained a 30% reduction in monthly migraine headache frequency from baseline;
4. It has been at least 12 weeks since the last injection of Botox®;
5. Botox® is not prescribed concurrently with injectable CGRP inhibitors (e.g., Aimovig®, Ajovy®, Emgality®);
6. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
7. If request is for a dose increase, new dose does not exceed 200 units per treatment session.

Approval duration
Medicaid: 168 days (two 12-week treatment sessions)
Commercial: 6 months

B. Esophageal Achalasia (off-label) (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria for the covered indications and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. It has been at least 24 weeks since the last injection of Botox®;
4. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;

5. If request is for a dose increase, new dose does not exceed 100 units per treatment session.

Approval duration
Medicaid: 168 days (single treatment session)
Commercial: 6 months

C. All Other Indications in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria for the covered indications and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. It has been at least 12 weeks since the last injection of Botox®;
4. Provider submits treatment plan detailing the quantity (in units) of Botox® to be injected in each muscle site, anticipated frequency of injection, and total dose per visit;
5. Meets (a or b):
   a. If request is for upper and/or lower limb spasticity and member is between 2 and 17 years of age, Botox® administration has not exceeded 8 Units/kg body weight or 300 Units over the last 3 months;
   b. For all other indications in this Section, Botox® administration has not exceeded 400 units over the last 3 months;
6. If request is for a dose increase, new dose should meet any one of the following (a-j):
   a. CD, CP: dose does not exceed 400 units per treatment session;
   b. Upper/lower limb spasticity (meets i ii or iii):
      i. Age 18 years of age or older: dose does not exceed 400 units per treatment session;
      ii. If age is 2 to 17 years of age, dose does not exceed 6 units/kg or 200 units (whichever is lower) per treatment session for upper limb spasticity;
      iii. If age is 2 to 17 years of age, dose does not exceed 8 units/kg or 300 units (whichever is lower) per treatment session for lower limb spasticity;
   c. Blepharospasm: dose does not exceed 5 units per muscle per treatment session and cumulative dose of 200 units total in a 30-day period;
   d. Strabismus, meets i or ii:
      i. Vertical and horizontal strabismus: dose does not exceed the lower of a two-fold increase or 25 units per muscle and 50 Units per treatment session;
      ii. VI nerve palsy: dose does not exceed the lower of a two-fold increase or 25 units per muscle and 25 units per treatment session;
   e. Oromandibular dystonia: 25 units per muscle per treatment session;
   f. Laryngeal dystonia (spasmodic dysphonia), upper extremity dystonia, upper extremity essential tremor : dose does not exceed 400 units per treatment session;
   g. Primary axillary hyperhidrosis: dose does not exceed 50 units per axilla per treatment session;
   h. Overactive bladder: dose does not exceed 100 units per treatment session;
   i. Urinary incontinence associated with neurologic condition: dose does not exceed 200 units per treatment session;
   j. Neurogenic detrusor overactivity: 200 units per treatment session;
   k. HD, IAS achalasia: Dose does not exceed 100 units per treatment session;
   l. Chronic anal fissure: Dose does not exceed 25 units per treatment session.

Approval duration
Medicaid: 84 days (single treatment session)
Commercial: 6 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

CD: Cervical dystonia
HD: Hirschsprung's disease
CP: Cerebral palsy
FDA: Food and Drugs Administration
IAS: Internal anal sphincter
MS: Multiple sclerosis
SCI: Spinal cord injury
TMD: Temporomandibular disorders
TMJ: Temporomandibular joint
OZ: Ounce
NDO: Neurogenic detrusor overactivity
OAB: Overactive bladder

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
carbidopa/levodopa (Sinemet®, Duopa®, Rytary®)	**Other Dystonias** (*see appendices C and D*) 25 mg/100 mg by mouth once daily, and increase by 1 tablet every 3 to 5 days.	1,200 mg/day of levodopa
Trihexyphenidyl	**Other Dystonias** (*see appendices C and D*) 30 mg by mouth once daily	30 mg/day
lactulose	**Hirschsprung's Disease, Internal Anal Sphincter Achalasia, Chronic anal fissure** 15-30 ml by mouth once daily	60 mL/day
Metamucil® (psyllium)	**Chronic anal fissure** One rounded tsp in 8 oz (ounce) liquid by mouth up to three times a day	3 doses/day
Dulcolax® (bisacodyl)	**Hirschsprung's Disease, Internal Anal Sphincter Achalasia, Chronic anal fissure** 5 to 15 mg by mouth or 10 mg per rectum once daily	30 mg/day
FiberCon® (Calcium polycarbophil)	**Chronic anal fissure** Two 625 mg tabs by mouth once daily- four times a day	5000 mg/day
Citrucel®(Methylcellulose)	**Chronic anal fissure** Caplet: 2 caplets up to 6 times daily Powder: 2 grams in 8 oz (ounce) of cold water by mouth up to 3 times daily	12 caplets/day or 6 grams/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
MiraLax®(Polyethyleneglycol 3350)	**Hirschsprung's Disease, Internal Anal Sphincter Achalasia, Chronic anal fissure** 17 grams of polyethylene glycol 3350 in 4-8 oz (ounce) water by mouth once daily	17 grams/day
Colace® (Docusate sodium)	**Hirschsprung's Disease, Internal Anal Sphincter Achalasia, Chronic anal fissure** 50-200 mg by mouth once daily-four times a day	200 mg/day
oxybutynin (Ditropan XL®, Gelnique®)	**Overactive Bladder** Immediate-release tablets: 5 mg orally two to three times daily Extended-release tablets: 5-10 mg orally once daily Topical gel: Apply contents of one sachet topically once daily	Immediate-release:20 mg/day Extended-release:30 mg/day Gel: one sachet/day
tolterodine tartrate (Detrol®/LA)	**Overactive Bladder** Immediate-release tablets: 2 mg orally twice daily Extended-release tablets: 4 mg orally once daily	4 mg/day
Myrbetriq® (mirabegron)	**Overactive Bladder** 25 mg orally once daily	50 mg/day
Anticonvulsants such as: divalproex (Depakote®), topiramate (Topamax®)	**Chronic Migraines** Refer to prescribing information	Refer to prescribing information
Beta blockers such as: propranolol (Inderal LA/XL®), metoprolol (Lopressor®), timolol	**Chronic Migraines** *Refer to prescribing information*	*Refer to prescribing information*
Antidepressants/tricyclic antidepressants such as: amitriptyline, venlafaxine (Effexor®)	**Chronic Migraines** *Refer to prescribing information*	*Refer to prescribing information*
Non-steroidal antiinflammatory drugs (NSAIDs) such as: fenoprofen (Nalfon®), ibuprofen, ketoprofen, naproxen (Naprosyn®)	**Chronic Migraines** *Refer to prescribing information*	*Refer to prescribing information*

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation;
  - Infection at the proposed injection site;

- Intradetrusor injections: urinary tract infection or urinary retention.

- Boxed Warning(s):
  - Distant spread of toxin effect;
  - 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.

APPENDIX D: General Information

- The potency units of botulinum toxin products are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of one product cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.
- Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) and is a Class III recommendation in Micromedex.
- Indication specific dosage and administration recommendations should be followed for Botox®. 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 interval.
- For detrusor overactivity associated with a neurologic condition there was no additional benefit of Botox® 300 Units over 200 Units.
- Safety and effectiveness have not been uniformly established for the treatment of temporomandibular disorders (TMD). Use of botulinumtoxin for this indication is a Class IIb recommendation in Micromedex based on a single study from 1999. A review of two clinical studies (from 2002 and 2011) (15 and 21 patients) found no significant differences in pain reduction between botulinumtoxin and placebo. Other small studies (from 2005 - Italy and 2008 - Turkey) have been performed and showed improvement in objective measures of pain (20 patients and 26 patients). The most common total dose of BTX-A used in the studies was 25u for each temporalis muscle and 50u for each masseter muscle. The studies did not repeat the dosing, but measured efficacy at 16 weeks post dose. The 2003 Guidelines for diagnosis and management of disorders involving the temporomandibular joint and related musculoskeletal structures mention Botox® as a possible treatment option for temporomandibular joint (TMJ) based on its mechanism of action and the pathophysiology of TMD.
  - TMD “gold standard” treatment continues to be: 1) TMJ intraoral orthotic; 2) Muscle relaxants by mouth; and 3) Home muscle relaxation exercises/techniques.
- Limb spasticity may be caused by heredity spastic paraplegia, multiple sclerosis or other demyelinating diseases of the central nervous system, spastic hemiplegia, infantile cerebral palsy, and stroke.
  *off-label uses

APPENDIX E: Definition and Classification of Dystonia

- Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned and twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.
- Dystonia is classified along two axes:
  - Clinical characteristics: Age at onset, body distribution, temporal pattern, associated features (additional movement disorders or neurological features) - the clinical characteristics fall into several

specific dystonia syndromes that help to guide diagnosis and treatment;
- Etiology: Nervous system pathology, inheritance.

APPENDIX F: Descriptions and Examples of Dystonia Syndromes*

Category	Subcategory	Description and Examples
Isolated dystonias	Early-onset generalized isolated dystonia	Dystonia with focal-onset in childhood often progresses to generalized involvement. Cases may be sporadic, familial, genetically defined or without known cause. • Early-onset generalized dystonia (DYT-TOR1A) • Adolescent-onset dystonia of mixed type (DYT-THAP1)
	Adult-onset focal or segmental isolated dystonia	Usually begins after age 30 years. Most are sporadic without identifiable cause. Rarely progress to generalized dystonia but can extend to contiguous body regions. • Adult-onset segmental dystonia (DYT-GNAL) • Cervical dystonia • Blepharospasm • Writer's cramp • Oromandibular dystonia • Laryngeal dystonia (spasmodic dysphonia) • Limb dystonia
Combined dystonias	Dystonia parkinsonism	Disorders that combine dystonia and parkinsonian features. May be accompanied by pyramidal tract involvement or nonmotor features including cognitive decline. Many are inherited. • Dopa-responsive dystonia (DYT-GCH1, DYT-TH, and DYT-SPR) • Wilson disease • Early-onset parkinsonism (PARK-PARKIN) • Conditions associated with neurodegeneration with brain iron accumulation
	Myclonusdystonia	Disorders in which there is a combination of dystonia and myoclonus. Dystonia may be mild and myoclonus generally predominates. • Myoclonus-dystonia (DYT-SGCE)

Category	Subcategory	Description and Examples
	Paroxysmal dyskinesia with dystonia	Disorders characterized by episodes of spontaneous or induced dyskinesia with dystonia. • Paroxysmal nonkinesigenic dyskinesia (DYT-MR1)

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	02/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title Table was updated. 2. Drug(s) Applied was updated. 3. Line of business policy applies was updated to All lines of business. 4. Dosing information was updated for dosing regimen of Blepharospasm, Cervical dystonia. 5. APPENDIX B: Therapeutic Alternatives were updated to remove Elavil®, Orudis® and Motrin® because of discontinuation. 6. APPENDIX B: "Therapeutic Alternatives verbiage was updated to Below are suggested therapeutic alternatives based on clinical guidance...." 7. Continued Therapy criteria II.A.1, B.1, C.1 were rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 8. Initial Approval criteria: Commercial duration were updated from member's renewal date to 6 months and Medicaid approval duration were updated in days.	12/03/2020	12/07/2020

9. Continued Approval criteria: Commercial duration were updated from member's renewal date to 6 months and Medicaid approval duration were updated in days. 10. References was reviewed and updated. 11. Updated I.D to include both upper and lower limb spasticity. 12. Updated I.D.3 age criteria. 13. Updated I.F.7 maximum dose from 200 units to 155 units. 14. Updated maximum dose and dosing regimens for migraine in Dosing Information table. 15. Added “headache specialist” to I.F.2. Added “and/or lower limb” to II.C.5.a.		
Policy was reviewed: 1. Background new indication added. 2. Dosing information updated for indication Neurogenic detrusor overactivity. 3. Initial Approval Criteria added. 4. Continued Therapy Approval updated in all other indications. 5. Appendix A: Abbreviation/Acronym Key added for NDO & OZ. 6. Appendix B: Therapeutic Alternatives abbreviated forms for PO, QID, TID, OZ, PR updated to full forms. 7. Updated initial approval criteria under I.A.7, I.H.1, I.D.1, I.D.5, I.E.4, I.B.6, I.C 8. Removed initial approval criteria section for “spasticity associated with cerebral palsy” and the same criteria is already laid out under section I.D 9. Added separate initial approval criteria for strabismus under section I.M 10. Updated appropriate dosing criteria under continuation of therapy 11. Updated the Dosing information table with appropriate regimen for each indication 12. References were reviewed and updated.	04/05/2021	06/10/2021