Clinical Policy: OnabotulinumtoxinA (Botox)

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Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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

FDA Approved Indication(s)

Indication	Adults	Pediatrics	Treatment	Prophylaxis
Overactive bladder	X		X	
Urinary incontinence	X		X	
Migraine	X			X
Upper/lower limb spasticity (includes CP)	X	X	X	
Cervical dystonia (focal dystonia)	X	X	X	
Axillary hyperhidrosis	X		X	
Blepharospasm (focal dystonia)	X	X	X	
Strabismus	X	X	X	
Off-Label Uses				
Laryngeal dystonia*	X		X	
Oromandibular dystonia*	X		X	
Upper extremity dystonia*	X	X	X	
Upper extremity essential tremor*	X		X	
Esophageal achalasia	X		X	
HD and IAS achalasia	X	X	X	
Chronic anal fissure	X		X	

Abbreviations: cerebral palsy (CP); Hirschsprung disease (HD), internal anal sphincter (IAS) achalasia.
**See criteria set entitled Focal Dystonia and Essential Tremor*

Botox 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
  - Urinary incontinence due to detrusor over-activity 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:
  - Upper and lower limb spasticity in adult patients
  - Upper limb spasticity in pediatric patients 2 to 17 years of age

- Lower limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy
- Cervical dystonia (CD) in adult patients, to reduce the severity of abnormal head position and neck pain
- Severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Blepharospasm associated with dystonia in patients ≥ 12 years of age
- Strabismus in patients ≥ 12 years of age

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

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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It is the policy of health plans affiliated with Centene Corporation® that Botox is **medically necessary** when one of the following criteria is met:

I. Initial Approval Criteria

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

1. Diagnosis of one of the following (a or b):
   a. OAB and member's history is positive for urinary urgency, frequency, and nocturia with or without incontinence;
   b. Urinary incontinence and member's history is positive for an associated neurologic condition (e.g., spinal cord injury, multiple sclerosis);
2. Prescribed by or in consultation with a neurologist or urologist;
3. Age ≥ 18 years;
4. Failure of a trial of at least two anticholinergic agents and one oral beta-3 agonist medication *(see Appendix B)*, each used for at least 30 days, unless clinically significant adverse effects are experienced or all are contraindicated;
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Request meets one of the following (a or b):
   a. OAB: Dose does not exceed 5 Units per injection and 100 Units per treatment session;
   b. Urinary incontinence associated with a neurologic condition: Dose does not exceed 6.7 Units per injection and 200 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

B. Chronic Migraine (must meet all):

1. Diagnosis of chronic migraine (i.e., ≥ 15 headache days per month for at least 3 months with headache lasting 4 hours a day or longer);
2. Prescribed by or in consultation with a neurologist or pain specialist;
3. Age ≥ 18 years;
4. Failure of an 8-week trial of at least two oral migraine preventive therapies *(see Appendix B)* from any of the following drug classes, unless clinically significant adverse effects are experienced or all are contraindicated (a, b, or c):
   a. Antiepileptics (e.g., divalproex sodium, sodium valproate, topiramate);
   b. Beta-blockers (e.g., metoprolol, propranolol, timolol);
   c. Antidepressants (e.g., amitriptyline, venlafaxine);
5. Member meets all of the following (a, b, and c):
   a. Botox is not prescribed concurrently with injectable CGRP inhibitors (e.g., Aimovig®, Ajovy®, Emgality®);
   b. Botox is not prescribed concurrently with other botulinum toxin products;
   c. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Dose does not exceed 5 Units per injection and 155 Units per treatment session.

Approval duration:

Medicaid/HIM – 24 weeks (two 12-week treatment sessions)
Commercial – 6 months or to member's renewal date, whichever is longer

C. Upper and Lower Limb Spasticity *(includes cerebral palsy)* (must meet all)**:**
1. Diagnosis of upper or lower limb spasticity (e.g., associated with paralysis, central nervous system demyelinating diseases such as multiple sclerosis, cerebral palsy, stroke);
2. Prescribed by or in consultation with a neurologist, orthopedist, or physiatrist;
3. Age ≥ 2 years;
4. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
5. Treatment plan details number of Units per injection site and treatment session;
6. Request meets one of the following (a or b):
   a. Age ≥ 18 years: Upper and/or lower limb: Dose not exceed 50 Units per injection and 400 Units per treatment session;
   b. Age 2 through 17 years (i, ii, and iii):
      i. Upper limb: Dose does not exceed 1 Unit/kg body weight per injection and the lower of 6 Units/kg body weight or 200 Units per treatment session;
      ii. Lower limb: Dose does not exceed 1 Unit/kg body weight per injection and the lower of 8 Units/kg body weight or 300 Units per treatment session.
      iii. If upper and lower limb spasticity are treated in the same treatment session, number of Units per treatment session does not exceed the lower of 10 Units/kg body weight or 340 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

D. Cervical Dystonia *(focal dystonia)* (must meet all):
1. Diagnosis of CD;
2. Prescribed by or in consultation with a neurologist, orthopedist, or physiatrist;
3. Age ≥ 16 years;
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, shoulders or head;
5. Contractions are causing pain and functional impairment;
6. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
7. Treatment plan details number of Units per injection site and treatment session;
8. Request meets one of the following (a or b):
   a. Age ≥ 18 years: Dose does not exceed 50 Units per injection, 100 Units total in the sternocleidomastoid (SCM) muscle, and 300 Units per treatment session;

b. Age 16 through 17 years: Dose does not exceed 50 Units per injection, 100 Units total in the SCM muscle, and the lower of 10 Units/kg body weight or 300 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

E. Primary Axillary Hyperhidrosis *(excessive underarm sweating)* (must meet all)**:**
**The treatment of hyperhidrosis is a benefit exclusion for HIM*

1. Diagnosis of primary axillary hyperhidrosis;
2. Prescribed by or in consultation with a neurologist or dermatologist;
3. Age ≥ 18 years;
4. Failure of a 6-month trial of topical aluminum chloride, unless contraindicated or clinically significant adverse effects are experienced;
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Dose does not exceed 50 Units per axilla and 100 Units per treatment session.

Approval duration:
Medicaid – 12 weeks (single treatment session)
HIM – Benefit Exclusion (Not Approvable)
Commercial – 6 months or to member's renewal date, whichever is longer

F. Blepharospasm *(focal dystonia - abnormal eyelid muscle contraction)* (must meet all)***:***

1. Diagnosis of blepharospasm;
2. Prescribed by or in consultation with a neurologist or ophthalmologist;
3. Age ≥ 12 years;
4. Member is experiencing significant disability in daily functional activities due to interference with vision;
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Dose does not exceed 2.5 Units per muscle, 7.5 Units per eye, and 15 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

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

1. Diagnosis of one of the following (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 < 20 prism diopters;
   ii. Horizontal strabismus 20 to 50 prism diopters;
c. Persistent sixth cranial nerve (VI; abducens nerve) palsy of ≥ one month involving the lateral rectus muscle;

2. Prescribed by or in consultation with a neurologist or ophthalmologist;
3. Age ≥ 12 years;
4. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
5. Treatment plan details number of Units per injection site and treatment session;
6. Request meets one of the following (a, b, or c):
   a. Vertical strabismus, or horizontal strabismus < 20 prism diopters: Dose does not exceed 2.5 Units per muscle and 5 Units per treatment session;
   b. Horizontal strabismus 20 to 50 prism diopters: Dose does not exceed 5 Units per muscle and 10 Units per treatment session;
   c. VI nerve palsy: Dose does not exceed 2.5 Units per treatment session (limited to treatment of one eye).

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

H. Focal Dystonia and Essential Tremor (off-label) (must meet all):

1. Diagnosis of one of the following (a, b, c, or d):
   a. Laryngeal dystonia;
   b. Oromandibular dystonia (OMD);
   c. Upper extremity (UE) dystonia;
   d. UE essential tremor;
2. Prescribed by or in consultation with a neurologist, ENT specialist, orthopedist, or physiatrist;
3. Age meets one of the following (a or b):
   a. For upper extremity dystonia: Age ≥ 2 years;
   b. For all other indications: Age ≥ 18 years;
4. For upper extremity dystonia: Failure of a trial of carbidopa/levodopa or trihexyphenidyl *(see Appendix B),* unless clinically significant adverse effects are experienced or both are contraindicated;
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Request meets one of the following (a or b):
   a. Laryngeal dystonia: Dose does not exceed 25 Units per treatment session;
   b. OMD/UE dystonia, UE 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; Units per treatment session does not exceed the lower of 10 Units/kg body weight or 340 Units for pediatrics, or 400 Units for adults*).

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

I. Esophageal Achalasia (off-label) (must meet all)**:**
1. Diagnosis of esophageal achalasia;
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 18 years;
4. Member is not a candidate for pneumatic dilation or laparoscopic surgical myotomy (e.g., due to age, comorbidity);
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Dose does not exceed 100 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

J. Hirschsprung Disease, Internal Anal Sphincter Achalasia (off-label) (must meet all):
1. Diagnosis of one of the following (a or b):
   a. Hirschsprung disease (HD) and (i or ii):
      i. Member has an HD subtype known as ultra-short segment HD;
      ii. Botox is prescribed for constipation post-surgery;
   b. Internal anal sphincter (IAS) achalasia;
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 2 years;
4. Failure of a trial of stool softeners and laxatives *(see Appendix B)*, unless clinically adverse effects are experienced or all are contraindicated;
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Dose does not exceed 100 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

K. Chronic Anal Fissure (off-label) (must meet all)**:**
1. Diagnosis of chronic anal fissure;
2. Prescribed by or in consultation with a gastroenterologist or colorectal surgeon;

3. Age ≥ 18 years;
4. Failure of nitroglycerin ointment and either oral/topical nifedipine or diltiazem *(see Appendix B)*, unless contraindicated or clinically significant adverse effects are experienced;
5. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
6. Treatment plan details number of Units per injection site and treatment session;
7. Dose does not exceed 25 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

L. Other diagnoses/indications:
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Approval

A. Chronic Migraine (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. If receipt of ≥ 2 Botox treatment sessions, member has experienced and maintained a 30% reduction in monthly migraine headache frequency from baseline;
3. Member meets all of the following (a, b, and c):
   a. Botox is not prescribed concurrently with injectable CGRP inhibitors (e.g., Aimovig, Ajovy, Emgality);
   b. Botox is not prescribed concurrently with other botulinum toxin products;
   c. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
4. Treatment plan details number of Units per injection site and treatment session;
5. If request is for a dose increase, new dose does not exceed 5 Units per injection and 155 Units per treatment session.

Approval duration:
Medicaid/HIM – 24 weeks (two 12-week treatment sessions)
Commercial – 6 months or to member's renewal date, whichever is longer

B. Esophageal Achalasia (must meet all):
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy;
3. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;

b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 24 weeks;
4. Treatment plan details number of Units per injection site and treatment session;
5. If request is for a dose increase, new dose does not exceed 100 Units per treatment session.

Approval duration:
Medicaid/HIM – 24 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

C. All Other Indications in Section I* (must meet all):
**The treatment of hyperhidrosis is a benefit exclusion for HIM*
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Member meets both of the following (a and b):
   a. Botox is not prescribed concurrently with other botulinum toxin products;
   b. Botulinum toxin therapy for cosmetic or medical conditions has not been administered within the last 12 weeks;
4. Treatment plan details number of Units per injection site and treatment session;
5. If request is for a dose increase, request meets one of the following (a through j):
   a. OAB: Dose does not exceed 5 Units per injection and 100 Units per treatment session;
   b. Urinary incontinence associated with a neurologic condition: Dose does not exceed 6.7 Units per injection and 200 Units per treatment session;
   c. Upper/lower limb spasticity (i or ii):
      i. Age ≥ 18 years: Upper and/or lower limb: Dose not exceed 50 Units per injection and 400 Units per treatment session;
      ii. Age 2 through 17 years (a, b, and c):
         a) Upper limb: Dose does not exceed 1 Unit/kg body weight per injection and the lower of 6 Units/kg body weight or 200 Units per treatment session;
         b) Lower limb: Dose does not exceed 1 Unit/kg body weight per injection and the lower of 8 Units/kg body weight or 300 Units per treatment session.
         c) If upper and lower limb spasticity are treated in the same treatment session, number of Units per treatment session does not exceed the lower of 10 Units/kg body weight or 340 Units per treatment session;
   d. CD (i or ii):
      i. Age ≥ 18 years: Dose does not exceed 50 Units per injection, 100 Units total in the SCM muscle, and 300 Units per treatment session;
      ii. Age 16 through 17 years: Dose does not exceed 50 Units per injection, 100 Units total in the SCM muscle, and the lower of 10 Units/kg body weight or 340 Units per treatment session;
   e. Primary axillary hyperhidrosis: Dose does not exceed 50 Units per axilla and 100 Units per treatment session;

f. Blepharospasm: Dose does not exceed 5 Units per muscle, 15 Units per eye, and 30 Units per treatment session;
g. Strabismus (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;
h. Focal dystonia and essential tremor (i or ii):
   i. Laryngeal dystonia: Dose does not exceed 25 Units per treatment session;
   ii. OMD/UE dystonia, UE 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; number of Units per treatment session does not exceed the lower of 10 Units/kg body weight or 340 Units for pediatrics, or 400 Units for adults*);
i. HD, IAS achalasia: Dose does not exceed 100 Units per treatment session;
j. Chronic anal fissure: Dose does not exceed 25 Units per treatment session.

Approval duration:
Medicaid/HIM – 12 weeks (single treatment session)
Commercial – 6 months or to member's renewal date, whichever is longer

D. Other diagnoses/indications (1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: 12 weeks (single treatment session); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;
B. Cosmetic treatment of hyperfunctional wrinkles of the upper face including glabellar frown lines, deep forehead wrinkles and periorbital wrinkles (crow's feet);
C. Episodic migraine (≤ 14 headache days per month): Safety and efficacy have not been established per the package insert;
D. Same-visit treatment of multiple indications with the exception of upper/lower limb spasticity.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CD: cervical dystonia
FDA: Food and Drugs Administration
HD: Hirschsprung disease
IAS: internal anal sphincter
MS: multiple sclerosis
OAB: overactive bladder

OMD: oromandibular dystonia
SCI: spinal cord injury
UE: upper extremity

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Overactive bladder, urinary incontinence		
oxybutynin (Ditropan®/XL, Gelnique®) *(anticholinergic agent)*	• 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) *(anticholinergic agent)*	• Immediate-release tablets: 2 mg orally twice daily • Extended-release tablets: 4 mg orally once daily	4 mg/day
Myrbetriq® (mirabegron) *(beta-3 agonist)*	25 mg orally once daily	50 mg/day
Chronic migraine		
Examples of oral migraine preventive therapies - • Anticonvulsants: divalproex (Depakote®), topiramate (Topamax®) • Beta blockers: propranolol (Inderal®), metoprolol (Lopressor®), timolol • Antidepressants/tricyclic antidepressants: amitriptyline (Elavil®), venlafaxine (Effexor®)	*Refer to prescribing information for dosing regimens.*	*Refer to prescribing information*
Primary axillary hyperhidrosis		
Drysol® (aluminum chloride)	Apply topically once daily	One application/day
Dystonia		
carbidopa/levodopa (Sinemet®, Duopa®, Rytary®)	25 mg/100 mg PO QD, and increase by 1 tablet every 3 to 5 days.	1,200 mg/day of levodopa

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
trihexyphenidyl	30 mg PO QD	30 mg/day
HD, IAS achalasia		
Dulcolax® (bisacodyl)	5 to 15 mg PO or 10 mg PR QD	30 mg/day
MiraLax® (Polyethylene glycol 3350)	17 grams of polyethylene glycol 3350 in 4-8 oz water by mouth once daily	17 grams/day
Colace® (Docusate sodium)	50-200 mg PO QD-QID	200 mg/day
Chronic anal fissure		
nitroglycerin 0.2% ointment (Rectiv®)	15 to 30 mg (2.5 to 5 cm as squeezed from the tube, about 1 to 2 inches), applied topically to skin every 8 hours while awake and at bedtime; application frequency may be increased to every 6 hours if needed; alternatively, a regimen providing a 12-hour nitrate-free interval may be used; apply dosage once each morning, then 6 hours later	75 mg (12.5 cm as squeezed from the tube)/day
nifedipine or diltiazem (oral or topical ointment/gel-compounded)	PO: At provider discretion Intra-anal: 0.2% ointment or gel, applied around fissure(s) 2 times daily for 6-8 weeks	Varies

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 and 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

Appendix D: Botulinum Toxin Product Interchangeability

- Potency Units of Botox are not interchangeable with other botulinum toxin product preparations (e.g., Dysport®, Myobloc®, Xeomin®).

Appendix E: Guideline Support for Off-Label Uses

Indication	Guideline
Focal Dystonia* and Essential Tremor	
Laryngeal dystonia	American Adacemy of Otolaryngology-Head and Neck Surgery Foundation (2018); American Academy of Neurology (2008)
Oromandibular dystonia	American Academy of Oral Medicine (2018)
Focal limb dystonia - UE**	American Academy of Neurology (2008)
Essential tremor - UE	American Academy of Neurology (2008)
Gastrointestinal Conditions *(see guidelines for required oral medication information)*	
Esophageal achalasia	American College of Gastroenterology (2013)
HD and IAS achalasia	American Pediatric Surgical Association (2017)
Chronic anal fissure	American College of Gastroenterology (2014)

**American Academy of Neurology (AAN) classifies Botox use for hemifacial spasm and motor tics as category C, and notes that data are inadequate to make a recommendation for lower limb dystonia. All other AAN Botox recommendations above are classified as category B - probably effective.*
***Policy criteria requiring failure of oral medication for dystonias are limited to dystonias affecting the limbs (see Cloud and Jinnah, 2010).*

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Adults: OAB	Up to 5 Units IM per injection across up to 20 injection sites in the detrusor muscle for a total of up to 100 Units per treatment session	See dosing regimens for maximum dose Frequency: • Esophageal acalasia: one treatment session every 24 weeks. • All other indications: one treatment session every 12 weeks.
Adults: urinary incontinence associated with neurologic condition	Up to approximately 6.7 Units IM per injection across up to 30 injection sites in the detrusor muscle for a total of up to 200 Units per treatment session	
Adults: chronic migraine	Up to 5 Units IM per injection across up to 7 head/neck muscles for a total of up to 155 Units per treatment session	
Adults: upper and lower limb spasticity	Up to 50 Units IM per injection and up to 400 Units per treatment session	
Pediatrics: upper and limb spasticity	• Upper limb spasticity: Up to the lower of 6 Units/kg or 200 Units IM per treatment session • Lower limb spasticity: Up to the lower of 8 Units/kg or 300 Units IM per treatment session • Upper and lower limb spasticity: Up to the lower of 10 Units/kg or 340 Units IM per treatment session	
Adults: CD	Up to 50 Units IM per injection, 100 Units total in the sternocleidomastoid (SCM) muscle, and 300 Units per treatment session	

Indication	Dosing Regimen	Maximum Dose
Pediatrics: CD	Up to 50 Units IM per injection, 100 Units total in the SCM muscle, and the lower of 10 Units/kg body weight or 300 Units per treatment session	
Adults: axillary hyperhidrosis	Up to 50 Units IM per axilla per treatment session	
Adults and pediatrics: blepharospasm	• Botox naive: Up to 2.5 Units IM per muscle, 7.5 Units per eye, and 15 Units per treatment session • Botox experienced: Up to 5 Units IM per muscle, 15 Units per eye, and 30 Units per treatment session	
Adults and pediatrics: strabismus	• Botox naive: ○ Vertical muscles, or horizontal strabismus < 20 prism diopters: Up to 2.5 Units IM per muscle and 5 Units per treatment session ○ Horizontal strabismus 20 to 50 prism diopters: Up to 5 Units IM per muscle and 10 Units per treatment session ○ VI nerve palsy: 2.5 Units IM in the medical rectus muscle and 2.5 Units per treatment session • Botox experienced: ○ Vertical and horizontal strabismus: Up to the lower of a two-fold increase or 25 Units IM per muscle and 50 Units per treatment session ○ VI nerve palsy: Up to the lower of a two-fold increase or 25 Units IM per muscle and 25 Units per treatment session	
Off-label uses		
Laryngeal dystonia	Up to 25 Units IM per treatment session (Micromedex, 2020)	
OMD UE dystonia UE 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; Number of Units per treatment session does not exceed the lower of 10 Units/kg body weight or 340 Units IM for pediatrics, or 400 Units IM for adults)	
Esophageal achalasia	Up to 100 Units IM per treatment session (Vaezi, et al., 2013	
HD, IAS achalasia	Up to 100 Units IM per treatment session (Langer, et al., 2017)	
Chronic anal fissure	Up to 25 Units IM per treatment session (Micromedex, 2020)	

VI. Product Availability

Vial: 100 Units, 200 Units

VII. References

1. Botox Prescribing Information. Irvine, CA: Allergan, Inc.; October 2019. Available at http://www.allergan.com/assets/pdf/botox_pi.pdf. Accessed February 17, 2020.
2. OnabotulinumtoxinA. In: Micromedex. Ann Arbor, MI: Truven Health Analytics; 2020. Available from: www.micromedexsolutions.com. Accessed February 17, 2020.

Overactive Bladder, Urinary Incontinence

3. Gormley EA, Lightner DJ, Faraday M, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. Journal of Urology. 2015; 193(5): 1572-1580.
4. Gormley EA, Lightner DJ, Burgio KL et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA (American Urological Association)/SUFU guideline. American Urological Association Education and Research, Inc. Available at http://www.auanet.org/education/guidelines/overactive-bladder.cfm. Published May 2014. Accessed January 25, 2019.

Migraine, Spasticity, Dystonia, Tremor

5. Silberstein SD, Holland S, Freitag F et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012; 78(17): 1337-1345.
6. Simpson DM, Hallett M, Ashman EJ et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016; 86(19): 1818-1826.
7. Simpson DM, Gracies JM, Graham HK et al. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008; 70(19): 1691-1698.
8. Simpson DM, Blitzer A, Brashear A et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008; 70: 1699-1706.
9. Stachler RJ, Francis DO, Schwartz SR, Damask CC, et al. Clinical practice guidelines: Hoarseness (Dysphonia) (Update). American Academy of Otolaryngology–Head and Neck Surgery Foundation 2018. 1-42. https://doi.org/10.1177/0194599817751030
10. France K, Stoopler ET. The American Academy of Oral Medicine clinical practice statement: Oromandibular dystonia. Oral Med Oral Pathol Oral Radiol, April 2018; 125 (4), 283-285.
11. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. June 15, 2013; 28(7): 863-873. doi:10.1002/mds.25475.
12. Cloud LJ, Jinnah HA. Treatment strategies for dystonia. Expert Opin Pharmacother 2010; 11(1):5-15.

Primary Axillary Hyperhidrosis,

13. Pariser DM, Ballard A. Topical therapies in hyperhidrosis care. Dermatol Clin. October 2014; 32(4): 485-90. doi: 10.1016/j.det.2014.06.008. Epub 2014 Jul 29.

Esophageal Achalasia
14. Vaezi MF, Pandolfino JE, Vela MF. American College of Gastroenterology clinical guideline: Diagnosis and management of achalasia. Am J Gastroenterol. 2013; 108(8): 1238-1259.

Hirschsprung Disease, Internal Anal Sphincter Achalasia
15. Langer JC, Rollins, MD, Levitt M. Guidelines for the management of postoperative obstructive symptoms in children with Hirschsprung disease. Pediatr Surg Int, 2017; 33:523-526. DOI 10.1007/s00383-017-4066-7

Chronic Anal Fissure
16. Wald A, Bharucha AE, Cosman BC, et al. American College of Gastroenterology clinical guideline: Management of benign anorectal disorders. Am J Gastroenterol 2014; 109:1141–1157; doi: 10.1038/ajg.2014.190; published online 15 July 2014.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0585	Injection, onabotulinumtoxinA, 1 unit

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from CP.PHAR.09. Added new FDA indication of lower limb spasticity per FDA labeling. Added compendial indication of laryngeal spasm/spasmodic dysphonia. -Overactive bladder: modified requirement for trial/failure of previous therapy to include oral beta-3 agonist medications per AUA guidelines. -Migraine: modified continuation criteria to require 30% reduction in headache frequency after 2 injections rather than just 1 per literature review and NICE guidelines. -Added general max dosing limit for cerebral palsy and spastic conditions and indication-specific max dosing limit for cervical dystonia, strabismus, primary axillary hyperhidrosis, upper limb spasticity, overactive bladder, urinary incontinence, and chronic migraine per PI. -Added indication-specific max dosing limit for chronic anal fissures, esophageal achalasia, laryngeal spasm/spasmodic dysphonia, Hirschsprung's disease, and dystonias per literature review. -Added prescriber requirement for overactive bladder, urinary incontinence, chronic migraines, upper limb spasticity, primary axillary hyperhidrosis, chronic anal fissures, cerebral palsy, esophageal achalasia, dystonias, Hirschsprung's disease, and spastic conditions.	05.16	07.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
-Added age restriction for upper limb spasticity and primary axillary hyperhidrosis per PI, and for chronic anal fissures, esophageal achalasia, and Hirschsprung's disease per literature review. -Added route of administration for each labeled indication per PI. -Removed reauthorization criteria requiring attestation of significant improvement in symptoms and/or health-related quality of life. Added positive response to therapy to continuation criteria.		
-Chronic migraine initial approval duration lengthened from 12 to 24 weeks (from one to two treatment sessions) to allow assessment of response as outlined in continuation criteria.	11.16	
The off-label criteria set entitled "Spastic Conditions" is deleted due to its broad scope; off-label requests not covered elsewhere in the policy are referred to the CP.PHAR.57.Global Biopharm policy so that they may be reviewed individually. Requirement that provider submits detailed treatment plan added to curtail abuse	02.17	
Indications reorganized. Definition of CD is edited per AAN guidelines. Laryngeal dystonia is merged with off-label dystonias which in turn are entitled "Other Dystonias". Clarified "blepharospasm" as a focal dystonia. Deleted causes and classifications of blepharospasm; blepharospasm and strabismus definitions are added. Dystonia information is added at Appendices B and C. Added esophageal achalasia definition. IAS achalasia is given its own line item. HD and IAS achalasia definitions added. Background FDA indication section and references categorized. "Non-cosmetic" parenthetical added to the background FDA indication section; cosmetic coverage restriction reworded under the "Other Diagnoses/Indications" section to include notation of glabellar lines.	06.17	07.17
2Q 2018 annual review: combined Medicaid and Commercial lines of business; added HIM line of business; expanded maximum dose for chronic migraine treatment to 200 units per treatment per 2012 NICE guidelines; Hirschsprung's Disease and Internal Anal Sphincter Achalasia: removed requirement for dietary and fluid control; added physical medicine and rehabilitation specialist for cervical dystonia, other dystonia, upper and lower limb spasticity, and spasticity associated with CP; added pain specialist for migraine; Medicaid: lowered age limit for CD to 16 from 18 years; added physiatrist to accepted specialist for spasticity associated with CP; Commercial: approval durations changed from length of benefit to 6 months or to member's renewal date, whichever is longer for initial and continued approval; references reviewed and updated.	04.24.18	05.18
2Q 2019 annual review: added requirement that Botox is not prescribed concurrently with injectable CGRP inhibitors; removed coverage for	01.15.19	05.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
hyperhidrosis for HIM due to benefit exclusion; references reviewed and updated.		
RT4: criteria added for newly FDA approved indication for pediatric extension of upper limb spasticity.	07.23.19	
RT4: criteria added for newly FDA approved indication for pediatric extension of lower limb spasticity; removed 2% specific strength requirement for nitroglycerin ointment due to availability reasons; added disclaimer regarding hyperhidrosis as a benefit exclusion for HIM on continued therapy section.	11.06.19	
2Q 2020 annual review: CP criteria incorporated under upper/lower limb spasticity; rehabilitation specialist incorporated under physiatrist; previous (last 12 weeks) or concurrent toxin product use restriction added to all initial/continuation criteria; off-label uses limited to those with guideline-based support (laryngeal dystonia, OMD, UE dystonia/essential tremor, HD, IAD, esophageal achalasia - Appendix E); dosing updated per package insert/off-label literature (Section V); initial approval duration shortened to 12 weeks for esophageal achalasia and CCB trial added for chronic anal fissure per guidelines; same-visit treatment for multiple indications is limited to upper/lower limb spasticity (Section III); references reviewed and updated.	03.02.20	05.20

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.