Botulinum Toxins A and B

Policy Number: 2026D0017AO
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➲ Instructions for Use

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Related Commercial Policies

- Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs
- Occipital Nerve Injections and Ablation (Including Occipital Neuralgia and Headache)
- Treatment of Temporomandibular Joint Disorders

Community Plan Policy

- Botulinum Toxins A and B

Coverage Rationale

➲ See Benefit Considerations

This policy refers to the following **botulinum toxin types A and B**:

- Dysport® (abobotulinumtoxinA)
- Daxxify® (daxibotulinumtoxinA-lanm)
- Xeomin® (incobotulinumtoxinA)
- Botox® (onabotulinumtoxinA)
- Myobloc® (rimabotulinumtoxinB)

Daxxify® is typically excluded from coverage. Coverage reviews may be in place if required by law or the benefit plan. Refer to the Medical Benefit Drug Policy titled Medical Benefit Therapeutic Equivalent Medications – Excluded Drugs and the corresponding excluded drug list with preferred alternatives.

Note: For requests that require medical necessity review, also refer to the General Requirements and Diagnosis-Specific Requirements sections below. (*For Medicare reviews, refer to the CMS section.**)

Coverage for Dysport®, Xeomin®, Botox®, Myobloc® is contingent on criteria in the General Requirements and Diagnosis-Specific Requirements sections.

General Requirements (Applicable to all Medical Necessity Requests)

- **All** of the following:
  - Diagnosis; **and**
  - Botulinum toxin administration is no more frequent than every 12 weeks, regardless of diagnosis; **and**
  - **One** of the following:
    - Prescriber attests dosing is in accordance with the U.S. Food and Drug Administration (FDA)–approved labeling; **or**
    - For indications without FDA-approved dosing, prescriber attests there is published clinical evidence to support the dosing

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Diagnosis-Specific Requirements

The information below indicates additional requirements for those indications having specific criteria in the list of proven indications and medically necessary indications.

Dysport (abobotulinumtoxinA) is proven in the treatment of the following conditions:

- **Achalasia**
- **Anal fissures, chronic**
- **Blepharospasm associated with dystonia**
- **Cervical dystonia (also known as spasmodic torticollis)**
- **Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease**
- **Essential tremor**
- **Hand dystonia (writer's, musician's, or typist's cramp)**
- **Hemifacial spasm (seventh cranial nerve disorders)**
- **Hyperhidrosis including gustatory sweating (i.e., Frey's syndrome)**
- **Oromandibular dystonia**
- **Sialorrhea**
- **Spasmodic dysphonia (i.e., laryngeal dystonia)**
- **Spasticity**
- **Strabismus**
- **Tongue dystonia**
- **Torsion dystonia**

Daxxify (daxibotulinumtoxinA-lanm) is proven in the treatment of the following condition:

- **Cervical dystonia (also known as spasmodic torticollis)**

Xeomin (incobotulinumtoxinA) is proven in the treatment of the following conditions:

- **Blepharospasm associated with dystonia**
- **Cervical dystonia (spasmodic torticollis)**
- **Sialorrhea**
- **Spasticity**

Botox (onabotulinumtoxinA) is proven in the treatment of the following conditions:

- **Achalasia**
- **Anal fissures, chronic**
- **Blepharospasm associated with dystonia**
- **Cervical dystonia (also known as spasmodic torticollis)**
- **Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease**
- **Essential tremor**
- **Hand dystonia (writer's, musician's, or typist's cramp)**
- **Hemifacial spasm (seventh cranial nerve disorders)**
- **Hyperhidrosis including gustatory sweating (i.e., Frey's syndrome)**
- **Migraine headache, chronic**
  Botox is proven for the prophylaxis of chronic migraine when the following criterion is met:
  - Diagnosis of chronic migraine defined by **all** of the following:
    - Greater than or equal to 15 headache days per month
    - Greater than or equal to 8 migraine days per month
    - Headaches last 4 hours per day or longer
- **Oromandibular dystonia**
- **Overactive bladder**
- **Sialorrhea**
- **Spasmodic dysphonia (i.e., laryngeal dystonia)**
- **Spasticity**
- **Strabismus**
- **Tongue dystonia**
- **Torsion dystonia**

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Myobloc (rimabotulinumtoxinB) is proven in the treatment of the following conditions:

- **Cervical dystonia (also known as spasmodic torticollis)**
  Additional information to support medical necessity review where applicable:
  Myobloc is medically necessary for the treatment of cervical dystonia when all of the following criteria are met:
  - For **initial therapy**, **all** of the following:
    - Diagnosis of cervical dystonia; **and**
    - History of failure, contraindication, or intolerance to **one** of the following:
      - Botox
      - Dysport
      - Xeomin

      and
    - Initial authorization will be for no more than 12 months
  - For **continuation of therapy**:
    - Reauthorization will be for no more than 12 months
- **Detrusor overactivity (also known as detrusor hyperreflexia)**
  Additional information to support medical necessity review where applicable:
  Myobloc is medically necessary for the treatment of detrusor overactivity when all of the following criteria are met:
  - For **initial therapy**, **all** of the following:
    - Diagnosis of detrusor overactivity; **and**
    - History of failure, contraindication, or intolerance to **one** of the following:
      - Botox
      - Dysport

      and
    - Initial authorization will be for no more than 12 months
  - For **continuation of therapy**:
    - Reauthorization will be for no more than 12 months
- **Sialorrhea**
  Additional information to support medical necessity review where applicable:
  Myobloc is medically necessary for the treatment of sialorrhea when all of the following criteria are met:
  - For **initial therapy**, **all** of the following:
  - Diagnosis of sialorrhea; **and**
    - History of failure, contraindication, or intolerance to **one** of the following:
      - Botox
      - Dysport
      - Xeomin

      and
    - Initial authorization will be for no more than 12 months
  - For **continuation of therapy**:
    - Reauthorization will be for no more than 12 months
- **Spasticity**
  Additional information to support medical necessity review where applicable:
  Myobloc is medically necessary for the treatment of spasticity when all of the following criteria are met:
  - For **initial therapy**, **all** of the following:
    - Diagnosis of spasticity; **and**
    - History of failure, contraindication, or intolerance to **one** of the following:
      - Botox
      - Dysport
      - Xeomin

      and
    - Initial authorization will be for no more than 12 months
  - For **continuation of therapy**:
    - Reauthorization will be for no more than 12 months

Unproven

Daxxify, Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of chronic migraine headache.

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Botox, Daxxify, Dysport, Myobloc, and Xeomin are unproven and not medically necessary for the treatment of the following conditions:

- Acquired nystagmus
- Anismus (pelvic floor dyssynergia)
- Benign prostatic hyperplasia
- Brachial plexus palsy
- Chronic daily headache
- Chronic low back pain
- Chronic prostatic pain
- Cricopharyngeal dysphagia (excludes achalasia)
- Epiphora following salivary gland transplantation
- Esophageal spasm
- Gastroparesis (including diabetic gastroparesis)
- Gustatory epiphora (crocodile tears)
- Lateral epicondylitis (tennis elbow)
- Lichen simplex
- Lower urinary tract (voiding) dysfunction
- Motor tics
- Myofascial pain syndrome
- Nasal hypersecretion
- Pain and/or wound healing after hemorrhoidectomy
- Pancreas divisum
- Piriformis syndrome
- Post-parotidectomy sialoceles
- Post-thoracotomy pseudoangina
- Proctalgia fugax
- Severe bruxism
- Severe paradoxical vocal cord movement
- Sphincter of Oddi dysfunction
- Temporomandibular disorders
- Tension-type headache
- Thyroid associated ophthalmopathy
- Tourette's syndrome
- Traumatic sixth nerve palsy
- Trigeminal neuralgia
- Trismus and stridor in amyotrophic lateral sclerosis

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

HCPCS Code	Description	Brand Name
J0585	Injection, onabotulinumtoxinA, 1 unit	Botox
J0586	Injection, abobotulinumtoxinA, 5 units	Dysport
J0587	Injection, rimabotulinumtoxinB, 100 units	Myobloc
J0588	Injection, incobotulinumtoxinA, 1 unit	Xeomin
J0589	Injection, daxibotulinumtoxina-lanm, 1 unit	Daxxify

Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles	X	X	X	X	
C71.1	Malignant neoplasm of frontal lobe	X	X	X	X	
C71.2	Malignant neoplasm of temporal lobe	X	X	X	X	
C71.3	Malignant neoplasm of parietal lobe	X	X	X	X	
C71.4	Malignant neoplasm of occipital lobe	X	X	X	X	
C71.5	Malignant neoplasm of cerebral ventricle	X	X	X	X	
C71.6	Malignant neoplasm of cerebellum	X	X	X	X	
C71.7	Malignant neoplasm of brain stem	X	X	X	X	
C71.8	Malignant neoplasm of overlapping sites of brain	X	X	X	X	
C71.9	Malignant neoplasm of brain, unspecified	X	X	X	X	
C72.0	Malignant neoplasm of spinal cord	X	X	X	X	
C72.1	Malignant neoplasm of cauda equina	X	X	X	X	
D33.0	Benign neoplasm of brain, supratentorial	X	X	X	X	
D33.1	Benign neoplasm of brain, infratentorial	X	X	X	X	

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
D33.2	Benign neoplasm of brain, unspecified	X	X	X	X	
D33.3	Benign neoplasm of cranial nerves	X	X	X	X	
D33.4	Benign neoplasm of spinal cord	X	X	X	X	
D33.7	Benign neoplasm of other specified parts of central nervous system	X	X	X	X	
D33.9	Benign neoplasm of central nervous system, unspecified	X	X	X	X	
D43.0	Neoplasm of uncertain behavior of brain, supratentorial	X	X	X	X	
D43.1	Neoplasm of uncertain behavior of brain, infratentorial	X	X	X	X	
D43.2	Neoplasm of uncertain behavior of brain, unspecified	X	X	X	X	
D43.3	Neoplasm of uncertain behavior of cranial nerves	X	X	X	X	
D43.4	Neoplasm of uncertain behavior of spinal cord	X	X	X	X	
D43.8	Neoplasm of uncertain behavior of other specified parts of central nervous system	X	X	X	X	
D43.9	Neoplasm of uncertain behavior of central nervous system, unspecified	X	X	X	X	
D49.6	Neoplasm of unspecified behavior of brain	X	X	X	X	
G04.1	Tropical spastic paraplegia	X	X	X	X	
G11.4	Hereditary spastic paraplegia	X	X	X	X	
G24.09	Other drug induced dystonia	X	X			
G24.1	Genetic torsion dystonia	X	X			
G24.2	Idiopathic nonfamilial dystonia	X	X			
G24.3	Spasmodic torticollis	X	X	X	X	X
G24.4	Idiopathic orofacial dystonia	X	X			
G24.5	Blepharospasm	X	X		X	
G24.8	Other dystonia	X	X			
G24.9	Dystonia, unspecified	X	X			
G25.0	Essential tremor	X	X			
G35.A	Relapsing-remitting multiple sclerosis	X	X	X	X	
G35.B0	Primary progressive multiple sclerosis, unspecified	X	X	X	X	
G35.B1	Active primary progressive multiple sclerosis	X	X	X	X	
G35.B2	Non-active primary progressive multiple sclerosis	X	X	X	X	
G35.C0	Secondary progressive multiple sclerosis, unspecified	X	X	X	X	
G35.C1	Active secondary progressive multiple sclerosis	X	X	X	X	
G35.C2	Non-active secondary progressive multiple sclerosis	X	X	X	X	
G35.D	Multiple sclerosis, unspecified	X	X	X	X	
G36.0	Neuromyelitis optica [Devic]	X	X	X	X	
G43.701	Chronic migraine without aura, not intractable, with status migrainosus	X				
G43.709	Chronic migraine without aura, not intractable, without status migrainosus	X				
G43.711	Chronic migraine without aura, intractable, with status migrainosus	X				

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
G43.719	Chronic migraine without aura, intractable, without status migrainosus	X				
G43.E01	Chronic migraine with aura, not intractable, with status migrainosus	X				
G43.E09	Chronic migraine with aura, not intractable, without status migrainosus	X				
G43.E11	Chronic migraine with aura, intractable, with status migrainosus	X				
G43.E19	Chronic migraine with aura, intractable, without status migrainosus	X				
G51.0	Bell's palsy	X	X			
G51.1	Geniculate ganglionitis	X	X			
G51.2	Melkersson's syndrome	X	X			
G51.31	Clonic hemifacial spasm, right	X	X			
G51.32	Clonic hemifacial spasm, left	X	X			
G51.33	Clonic hemifacial spasm, bilateral	X	X			
G51.39	Clonic hemifacial spasm, unspecified	X	X			
G51.4	Facial myokymia	X	X			
G51.8	Other disorders of facial nerve	X	X			
G51.9	Disorder of facial nerve, unspecified	X	X			
G80.0	Spastic quadriplegic cerebral palsy	X	X	X	X	
G80.1	Spastic diplegic cerebral palsy	X	X	X	X	
G80.2	Spastic hemiplegic cerebral palsy	X	X	X	X	
G80.3	Athetoid cerebral palsy	X	X	X	X	
G80.4	Ataxic cerebral palsy	X	X	X	X	
G80.8	Other cerebral palsy	X	X	X	X	
G80.9	Cerebral palsy, unspecified	X	X	X	X	
G81.10	Spastic hemiplegia affecting unspecified side	X	X	X	X	
G81.11	Spastic hemiplegia affecting right dominant side	X	X	X	X	
G81.12	Spastic hemiplegia affecting left dominant side	X	X	X	X	
G81.13	Spastic hemiplegia affecting right nondominant side	X	X	X	X	
G81.14	Spastic hemiplegia affecting left nondominant side	X	X	X	X	
G83.4	Cauda equina syndrome	X	X	X		
H49.00	Third [oculomotor] nerve palsy, unspecified eye	X	X			
H49.01	Third [oculomotor] nerve palsy, right eye	X	X			
H49.02	Third [oculomotor] nerve palsy, left eye	X	X			
H49.03	Third [oculomotor] nerve palsy, bilateral	X	X			
H49.10	Fourth [trochlear] nerve palsy, unspecified eye	X	X			
H49.11	Fourth [trochlear] nerve palsy, right eye	X	X			
H49.12	Fourth [trochlear] nerve palsy, left eye	X	X			
H49.13	Fourth [trochlear] nerve palsy, bilateral	X	X			
H49.20	Sixth [abducent] nerve palsy, unspecified eye	X	X			
H49.21	Sixth [abducent] nerve palsy, right eye	X	X			
H49.22	Sixth [abducent] nerve palsy, left eye	X	X			
H49.23	Sixth [abducent] nerve palsy, bilateral	X	X			

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
H49.30	Total (external) ophthalmoplegia, unspecified eye	X	X			
H49.31	Total (external) ophthalmoplegia, right eye	X	X			
H49.32	Total (external) ophthalmoplegia, left eye	X	X			
H49.33	Total (external) ophthalmoplegia, bilateral	X	X			
H49.40	Progressive external ophthalmoplegia, unspecified eye	X	X			
H49.41	Progressive external ophthalmoplegia, right eye	X	X			
H49.42	Progressive external ophthalmoplegia, left eye	X	X			
H49.43	Progressive external ophthalmoplegia, bilateral	X	X			
H49.811	Kearns-Sayre syndrome, right eye	X	X			
H49.812	Kearns-Sayre syndrome, left eye	X	X			
H49.813	Kearns-Sayre syndrome, bilateral	X	X			
H49.881	Other paralytic strabismus, right eye	X	X			
H49.882	Other paralytic strabismus, left eye	X	X			
H49.883	Other paralytic strabismus, bilateral	X	X			
H49.889	Other paralytic strabismus, unspecified eye	X	X			
H49.9	Unspecified paralytic strabismus	X	X			
H50.00	Unspecified esotropia	X	X			
H50.011	Monocular esotropia, right eye	X	X			
H50.012	Monocular esotropia, left eye	X	X			
H50.021	Monocular esotropia with A pattern, right eye	X	X			
H50.022	Monocular esotropia with A pattern, left eye	X	X			
H50.031	Monocular esotropia with V pattern, right eye	X	X			
H50.032	Monocular esotropia with V pattern, left eye	X	X			
H50.041	Monocular esotropia with other noncomitancies, right eye	X	X			
H50.042	Monocular esotropia with other noncomitancies, left eye	X	X			
H50.05	Alternating esotropia	X	X			
H50.06	Alternating esotropia with A pattern	X	X			
H50.07	Alternating esotropia with V pattern	X	X			
H50.08	Alternating esotropia with other noncomitancies	X	X			
H50.10	Unspecified exotropia	X	X			
H50.111	Monocular exotropia, right eye	X	X			
H50.112	Monocular exotropia, left eye	X	X			
H50.121	Monocular exotropia with A pattern, right eye	X	X			
H50.122	Monocular exotropia with A pattern, left eye	X	X			
H50.131	Monocular exotropia with V pattern, right eye	X	X			
H50.132	Monocular exotropia with V pattern, left eye	X	X			
H50.141	Monocular exotropia with other noncomitancies, right eye	X	X			
H50.142	Monocular exotropia with other noncomitancies, left eye	X	X			
H50.15	Alternating exotropia	X	X			
H50.16	Alternating exotropia with A pattern	X	X			

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
H50.17	Alternating exotropia with V pattern	X	X			
H50.18	Alternating exotropia with other noncomitancies	X	X			
H50.21	Vertical strabismus, right eye	X	X			
H50.22	Vertical strabismus, left eye	X	X			
H50.30	Unspecified intermittent heterotropia	X	X			
H50.311	Intermittent monocular esotropia, right eye	X	X			
H50.312	Intermittent monocular esotropia, left eye	X	X			
H50.32	Intermittent alternating esotropia	X	X			
H50.331	Intermittent monocular exotropia, right eye	X	X			
H50.332	Intermittent monocular exotropia, left eye	X	X			
H50.34	Intermittent alternating exotropia	X	X			
H50.40	Unspecified heterotropia	X	X			
H50.411	Cyclotropia, right eye	X	X			
H50.412	Cyclotropia, left eye	X	X			
H50.42	Monofixation syndrome	X	X			
H50.43	Accommodative component in esotropia	X	X			
H50.50	Unspecified heterophoria	X	X			
H50.51	Esophoria	X	X			
H50.52	Exophoria	X	X			
H50.53	Vertical heterophoria	X	X			
H50.54	Cyclophoria	X	X			
H50.55	Alternating heterophoria	X	X			
H50.60	Mechanical strabismus, unspecified	X	X			
H50.611	Brown's sheath syndrome, right eye	X	X			
H50.612	Brown's sheath syndrome, left eye	X	X			
H50.621	Inferior oblique muscle entrapment, right eye	X	X			
H50.622	Inferior oblique muscle entrapment, left eye	X	X			
H50.629	Inferior oblique muscle entrapment, unspecified eye	X	X			
H50.631	Inferior rectus muscle entrapment, right eye	X	X			
H50.632	Inferior rectus muscle entrapment, left eye	X	X			
H50.639	Inferior rectus muscle entrapment, unspecified eye	X	X			
H50.641	Lateral rectus muscle entrapment, right eye	X	X			
H50.642	Lateral rectus muscle entrapment, left eye	X	X			
H50.649	Lateral rectus muscle entrapment, unspecified eye	X	X			
H50.651	Medial rectus muscle entrapment, right eye	X	X			
H50.652	Medial rectus muscle entrapment, left eye	X	X			
H50.659	Medial rectus muscle entrapment, unspecified eye	X	X			
H50.661	Superior oblique muscle entrapment, right eye	X	X			
H50.662	Superior oblique muscle entrapment, left eye	X	X			
H50.669	Superior oblique muscle entrapment, unspecified eye	X	X			
H50.671	Superior rectus muscle entrapment, right eye	X	X			
H50.672	Superior rectus muscle entrapment, left eye	X	X			
H50.679	Superior rectus muscle entrapment, unspecified eye	X	X			

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
H50.681	Extraocular muscle entrapment, unspecified, right eye	X	X			
H50.682	Extraocular muscle entrapment, unspecified, left eye	X	X			
H50.689	Extraocular muscle entrapment, unspecified, unspecified eye	X	X			
H50.69	Other mechanical strabismus	X	X			
H50.811	Duane's syndrome, right eye	X	X			
H50.812	Duane's syndrome, left eye	X	X			
H50.89	Other specified strabismus	X	X			
H50.9	Unspecified strabismus	X	X			
H51.0	Palsy (spasm) of conjugate gaze	X	X			
I60.10	Nontraumatic subarachnoid hemorrhage from unspecified middle cerebral artery	X	X	X	X	
I60.11	Nontraumatic subarachnoid hemorrhage from right middle cerebral artery	X	X	X	X	
I60.12	Nontraumatic subarachnoid hemorrhage from left middle cerebral artery	X	X	X	X	
I61.0	Nontraumatic intracerebral hemorrhage in hemisphere, subcortical	X	X	X	X	
I61.1	Nontraumatic intracerebral hemorrhage in hemisphere, cortical	X	X	X	X	
I61.2	Nontraumatic intracerebral hemorrhage in hemisphere, unspecified	X	X	X	X	
I61.3	Nontraumatic intracerebral hemorrhage in brain stem	X	X	X	X	
I61.4	Nontraumatic intracerebral hemorrhage in cerebellum	X	X	X	X	
I61.5	Nontraumatic intracerebral hemorrhage, intraventricular	X	X	X	X	
I61.6	Nontraumatic intracerebral hemorrhage, multiple localized	X	X	X	X	
I61.8	Other nontraumatic intracerebral hemorrhage	X	X	X	X	
I61.9	Nontraumatic intracerebral hemorrhage, unspecified	X	X	X	X	
I63.00	Cerebral infarction due to thrombosis of unspecified precerebral artery	X	X	X	X	
I63.011	Cerebral infarction due to thrombosis of right vertebral artery	X	X	X	X	
I63.012	Cerebral infarction due to thrombosis of left vertebral artery	X	X	X	X	
I63.013	Cerebral infarction due to thrombosis of bilateral vertebral arteries	X	X	X	X	
I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery	X	X	X	X	
I63.02	Cerebral infarction due to thrombosis of basilar artery	X	X	X	X	
I63.031	Cerebral infarction due to thrombosis of right carotid artery	X	X	X	X	

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
I63.032	Cerebral infarction due to thrombosis of left carotid artery	X	X	X	X	
I63.033	Cerebral infarction due to thrombosis of bilateral carotid arteries	X	X	X	X	
I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery	X	X	X	X	
I63.09	Cerebral infarction due to thrombosis of other precerebral artery	X	X	X	X	
I63.10	Cerebral infarction due to embolism of unspecified precerebral artery	X	X	X	X	
I63.111	Cerebral infarction due to embolism of right vertebral artery	X	X	X	X	
I63.112	Cerebral infarction due to embolism of left vertebral artery	X	X	X	X	
I63.113	Cerebral infarction due to embolism of bilateral vertebral arteries	X	X	X	X	
I63.119	Cerebral infarction due to embolism of unspecified vertebral artery	X	X	X	X	
I63.12	Cerebral infarction due to embolism of basilar artery	X	X	X	X	
I63.131	Cerebral infarction due to embolism of right carotid artery	X	X	X	X	
I63.132	Cerebral infarction due to embolism of left carotid artery	X	X	X	X	
I63.133	Cerebral infarction due to embolism of bilateral carotid arteries	X	X	X	X	
I63.139	Cerebral infarction due to embolism of unspecified carotid artery	X	X	X	X	
I63.19	Cerebral infarction due to embolism of other precerebral artery	X	X	X	X	
I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries	X	X	X	X	
I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral artery	X	X	X	X	
I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral artery	X	X	X	X	
I63.213	Cerebral infarction due to unspecified occlusion or stenosis of bilateral vertebral arteries	X	X	X	X	
I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral artery	X	X	X	X	
I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar artery	X	X	X	X	
I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries	X	X	X	X	
I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries	X	X	X	X	
I63.233	Cerebral infarction due to unspecified occlusion or stenosis of bilateral carotid arteries	X	X	X	X	
I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid artery	X	X	X	X	

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries	X	X	X	X	
I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery	X	X	X	X	
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery	X	X	X	X	
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery	X	X	X	X	
I63.313	Cerebral infarction due to thrombosis of bilateral middle cerebral arteries	X	X	X	X	
I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery	X	X	X	X	
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery	X	X	X	X	
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery	X	X	X	X	
I63.323	Cerebral infarction due to thrombosis of bilateral anterior cerebral arteries	X	X	X	X	
I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery	X	X	X	X	
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery	X	X	X	X	
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery	X	X	X	X	
I63.333	Cerebral infarction due to thrombosis of bilateral posterior cerebral arteries	X	X	X	X	
I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery	X	X	X	X	
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery	X	X	X	X	
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery	X	X	X	X	
I63.343	Cerebral infarction due to thrombosis of bilateral cerebellar arteries	X	X	X	X	
I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery	X	X	X	X	
I63.39	Cerebral infarction due to thrombosis of other cerebral artery	X	X	X	X	
I63.40	Cerebral infarction due to embolism of unspecified cerebral artery	X	X	X	X	
I63.411	Cerebral infarction due to embolism of right middle cerebral artery	X	X	X	X	
I63.412	Cerebral infarction due to embolism of left middle cerebral artery	X	X	X	X	
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries	X	X	X	X	
I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery	X	X	X	X	
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery	X	X	X	X	

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery	X	X	X	X	
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries	X	X	X	X	
I63.429	Cerebral infarction due to embolism of unspecified anterior cerebral artery	X	X	X	X	
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery	X	X	X	X	
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery	X	X	X	X	
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries	X	X	X	X	
I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery	X	X	X	X	
I63.441	Cerebral infarction due to embolism of right cerebellar artery	X	X	X	X	
I63.442	Cerebral infarction due to embolism of left cerebellar artery	X	X	X	X	
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries	X	X	X	X	
I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery	X	X	X	X	
I63.49	Cerebral infarction due to embolism of other cerebral artery	X	X	X	X	
I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery	X	X	X	X	
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery	X	X	X	X	
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery	X	X	X	X	
I63.513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle cerebral arteries	X	X	X	X	
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery	X	X	X	X	
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery	X	X	X	X	
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery	X	X	X	X	
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior cerebral arteries	X	X	X	X	
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery	X	X	X	X	
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery	X	X	X	X	
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery	X	X	X	X	
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior cerebral arteries	X	X	X	X	
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery	X	X	X	X	

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery	X	X	X	X	
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery	X	X	X	X	
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries	X	X	X	X	
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery	X	X	X	X	
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery	X	X	X	X	
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic	X	X	X	X	
I63.81	Other cerebral infarction due to occlusion or stenosis of small artery	X	X	X	X	
I63.89	Other cerebral infarction	X	X	X	X	
I63.9	Cerebral infarction, unspecified	X	X	X	X	
J38.5	Laryngeal spasm	X	X			
K11.7	Disturbances of salivary secretion	X	X	X	X	
K22.0	Achalasia of cardia	X	X			
K60.1	Chronic anal fissure	X	X			
L74.510	Primary focal hyperhidrosis, axilla	X	X			
L74.511	Primary focal hyperhidrosis, face	X	X			
L74.512	Primary focal hyperhidrosis, palms	X	X			
L74.513	Primary focal hyperhidrosis, soles	X	X			
L74.519	Primary focal hyperhidrosis, unspecified	X	X			
L74.52	Secondary focal hyperhidrosis	X	X			
N31.0	Uninhibited neuropathic bladder, not elsewhere classified	X	X	X		
N31.1	Reflex neuropathic bladder, not elsewhere classified	X	X	X		
N31.9	Neuromuscular dysfunction of bladder, unspecified	X	X	X		
N32.81	Overactive bladder	X				
N36.44	Muscular disorders of urethra	X	X	X		
N39.41	Urge incontinence	X				
N39.46	Mixed incontinence	X				
R13.12	Dysphagia, oropharyngeal phase	X	X			
R25.0	Abnormal head movements	X	X	X	X	
R25.1	Tremor, unspecified	X	X	X	X	
R25.2	Cramp and spasm	X	X	X	X	
R25.3	Fasciculation	X	X	X	X	
R25.8	Other abnormal involuntary movements	X	X	X	X	
R25.9	Unspecified abnormal involuntary movements	X	X	X	X	
R49.0	Dysphonia	X	X			
R49.9	Unspecified voice and resonance disorder	X	X			
R61	Generalized hyperhidrosis	X	X			
Z85.841	Personal history of malignant neoplasm of brain	X	X	X	X	

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Diagnosis Code	Description	Applies to HCPCS Code				
		J0585	J0586	J0587	J0588	J0589
Z85.848	Personal history of malignant neoplasm of other parts of nervous tissue	X	X	X	X	
Z87.820	Personal history of traumatic brain injury	X	X	X	X	

Background

There are seven serologically distinct forms of botulinum toxin, A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain. They all inhibit acetylcholine release at the neuromuscular junction via the enzymatic inactivation of a protein that is required for the docking and fusion process involved in the release of acetylcholine. Each neurotoxin works at a distinct site. Botulinum toxin type A cleaves the protein SNAP-25 and botulinum toxin type B cleaves synaptobrevin, both of these proteins are part of a protein complex necessary for proper docking and fusion. The potency units of botulinum toxins are specific to the preparation and assay method utilized. They are not interchangeable and, therefore, the units of biological activity cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Benefit Considerations

Botulinum toxin type A and B are cosmetic when used to improve appearance, or in the absence of physiological functional impairment that would be improved by their use. Most UnitedHealthcare Certificates of Coverage (COCs) and Summary Plan Descriptions (SPDs) exclude benefit coverage for cosmetic services. In addition, most certificates of coverage and many summary plan descriptions explicitly exclude benefit coverage for medical and surgical treatment of excessive sweating (hyperhidrosis). The member specific benefit plan document must be reviewed to determine what benefits, if any, exist for treatment of hyperhidrosis.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Clinical Evidence

Proven

Cervical Dystonia

In a randomized, double-blind, multicenter, non-inferiority, two-period crossover study, Yun et al compared the efficacy and safety of Dysport and Botox at a 2.5:1 ratio in the treatment of cervical dystonia (CD). The lower ratio than 3:1 was suggested as a more appropriate conversion ratio, due to the higher efficacy of Botox and more frequent incidence of adverse effects in CD and other focal movement disorders. Patients who were over 20 years old and have experienced CD for at least 18 months were eligible, and were allowed to continue on a stable dose of medications for CD for the duration of the trial. Both products were diluted so that the 2.5:1 ratio resulted in the same volume to be administered. The patients received either Dysport or Botox and were followed monthly for the first 16 weeks. After the 4-week washout period, each group was crossed over to receive the other product, respectively. Patients were also followed up with monthly for 16 weeks in the second period. Results from both periods were merged and compared according to the two different products. The primary efficacy outcome was the change in the Tsui scale between the baseline value and that at 1 month after each injection (peak effect). One hundred and two patients enrolled in the study. Patients were allocated 49 and 53 to two different arms of the trial. Arm 1 received Dysport during the first phase and Botox during the crossover phase. Arm 2 received Botox during the first phase and Dysport during the second phase. Only 94 of the 102 patients completed the entire study and were included in the final analysis. Mean changes in the Tsui scale between baseline and 4 weeks after each injection trended to favor Botox, however, this was not statistically significant (4.0 ±3.9 points Dysport vs. 4.8 ±4.1 points for Botox; 95% CI, -0.1-1.7; p = 0.091). The mean change of the Toronto western spasmodic torticollis rating scale score, the proportion of improvement in clinical global impression and patient global impression, and the incidences of adverse events were not significantly different between the two treatments. The authors concluded that, in terms of efficacy and safety, Dysport at a ratio of 2.5:1 to Botox was not inferior to Botox in patients with CD.

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The efficacy of Daxxify was evaluated in a randomized, double-blind, placebo-controlled, multicenter trial in a total of 301 patients (NCT03608397). At study baseline, 84% of patients had previously received a botulinum toxin as treatment for cervical dystonia. Patients had a clinical diagnosis of cervical dystonia with baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ≥ 20, TWSTRS severity score ≥ 15, TWSTRS disability score ≥ 3, and TWSTRS pain score ≥ 1. For patients who had previously received a botulinum toxin treatment for cervical dystonia, the trial required that ≥ 14 weeks had passed since the most recent botulinum toxin administration. Patients were randomized (3:3:1) to receive a single administration of 2.5 mL of either Daxxify 125 Units (n = 125), Daxxify 250 Units (n = 130), or placebo (n = 46), divided amongst the affected muscles as selected by the investigator. The primary efficacy endpoint was the mean change in the TWSTRS total score from baseline averaged over weeks 4 and 6. TWSTRS evaluates the severity of dystonia, patient-perceived disability from dystonia, and pain, with a range of possible scores from 0 to 85. The mean change from baseline in the total TWSTRS score was significantly greater for both dosage groups of Daxxify than for placebo.

Detrusor Overactivity

In a prospective, long-term (3 year), multicenter, open-label extension study following a 52-week, phase III trial of onabotulinumtoxinA, patients were treated on an "as needed" basis with intradetrusor onabotulinumtoxinA (200U or 300U) for urinary incontinence (UI) due to neurogenic detrusor overactivity. Patients received treatment ≥ 12 weeks since the previous treatment and a UI episode threshold. The primary efficacy endpoint was the change from study baseline in UI episodes/day at week 6 after each treatment. Additional efficacy measurements included: percent change in UI episodes, the proportions of patients with ≥ 50% and 100% reductions from baseline in UI episodes/day, changes from baseline in volume/void and Incontinence Quality of Life (I-QOL) total summary scores, IQOL responder rates (proportion of patients achieving a ≥ 11-point increase from baseline in I-QOL total score, which is defined as the minimally important difference for I-QOL in NDO), and duration of treatment effect (time to patient request for retreatment). OnabotulinumtoxinA 200U consistently reduced UI episodes/day; reductions from baseline ranged from -3.2 to -4.1 across six treatments. Volume/void consistently increased, nearly doubling after treatment. I-QOL improvements were consistently greater than twice the minimally important difference (+11 points). Overall median duration of effect was 9.0 months (200U). Results were similar for onabotulinumtoxinA 300U. Most common AEs were urinary tract infections and urinary retention. De novo CIC rates were 29.5, 3.4, and 6.0% (200U), and 43.0, 15.0, and 4.8% (300U) for treatments 1-3, respectively; de novo CIC rates were 0% for treatments 4-6. The authors concluded that OnabotulinumtoxinA treatments consistently improve UI, volume/void, and QOL in patients with UI due to NDO in this 4-year study, with no new safety signals.

Migraine Headache

OnabotulinumtoxinA is beneficial for the prophylaxis of chronic migraine headaches based upon FDA approval, published practice guidelines, professional society evidence reviews, randomized controlled clinical trials, and smaller randomized exploratory studies.

Aurora et al performed a secondary analysis of the data to assess patients who received all five treatment cycles and completed the PREEMPT-1 and PREEMPT-2 trials. Both studies were 24 week double-blind, placebo controlled, parallel-group phase, with a 32-week open-label phase, that evaluated the efficacy and safety of onabotulinumtoxinA (BoNT-A). Out of a total of 1,384 total patients, 1,005 received all five treatment cycles and were included in the analysis. Of these, 513 received all 5 cycles with BTA, whereas 492 underwent 2 cycles of placebo followed by 3 cycles of BoNT-A treatment. After 56 weeks of treatment, significant between group differences were found favoring BoNT-A treatment vs. placebo, even after those receiving placebo switching to BoNT-A. The following headache symptoms were evaluated: mean change in frequency of headache days (-12.0 vs -11.0, p = 0.035); total migraine days (-11.6 vs -10.7, p = 0.038), and moderate/severe headache days (-11.0 vs -10.1 n = 0.042). There were also large mean improvements from baseline in the following measures: cumulative hours of headache on headache days, frequency of headache episodes, percentage with severe Headache Impact Test (HIT)-6 scores, and total HIT-6 and Migraine-Specific Quality of Life Questionnaire scores. The percent of patients with a ≥ 50% reduction from baseline in frequency of headache days was significantly greater for the BoNT-A only group at week 56 (69.6% vs 62.8%, p = 0.023). Treatment-related adverse event rates were 28.5% for the BoNT-A group vs. 12.4% for the placebo group during the double-blind phase of the trials. The most frequently reported treatment related adverse events were neck pain (4.3%), muscular weakness (1.6%), injection site pain (2.1%), and eyelid ptosis (1.9%). This data supports the use of onabotulinumtoxinA for the treatment of migraine headaches.

In a follow up analysis of the PREEMPT clinical trials, Lipton et al., assessed the effects of treatment with onabotulinumtoxinA on health-related quality of life (HRQoL) and headache impact in adults with chronic migraine. In the PREEMPT trials, Headache Impact Test (HIT)-6 scores were obtained at baseline and every 4 weeks. In terms of change in total HIT-6 scores, a negative value reflects reduced headache impact and an improvement in the patient's functionality. HRQoL was measured by the Migraine-Specific Quality of Life Questionnaire (MSQ v2.1). This score was

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obtained at baseline and every 12 weeks. A positive change in MSQ v2.1 scores reflects improvement in HRQoL during the PREEMPT study. An analysis of the combined data looked at 688 subjects who received treatment with Botox vs. 696 who received saline placebo injections. Baseline mean total HIT-6 and MSQ v2.1 scores were comparable between groups; 93.1% were severely impacted based on HIT-6 scores ≥ 60. At 24 weeks, in comparison with placebo, Botox treatment significantly reduced HIT-6 scores at all time periods during the double-blind phase of the trials ($p \leq 0.014$). Additionally, HIT-6 measures of headache impact scores showed significant benefit for the Botox group at 24 weeks of treatment ($p < 0.001$). Botox treatment significantly improved all domains of the MSQ v2.1 at 24 weeks ($p < 0.001$). There was also a significant benefit shown for the Botox group compared to placebo with regard to the proportion of subjects who received clinically meaningful reduction in the number of headache days at all-time points in the double-blind study periods ($p \leq 0.025$). The authors concluded that Botox treatment reduces headache impact and improves HRQoL.

The pooled results of two phase 3, randomized, double-blind, multicenter, placebo-controlled trials addressing the use of botulinum toxin for the treatment of chronic migraine headaches were reported by Dodick et al., in 2010.These studies were from the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) clinical program, involving a 24-week randomized, double-blind phase followed by a 32-week open-label phase. Subjects were randomized (1:1) to receive either 155 units of onabotulinumtoxinA (BoNT-A) or placebo injections every 12 weeks. A total of 1384 adult patients were randomized to onabotulinumtoxinA (n = 688) or placebo (n = 696), with study visits every 4 weeks. Both studies were identical in design, with the exception being the designation of the primary (mean change from baseline in frequency of headache days for the 28-day period ending with week 24) and secondary endpoints (frequency of migraine days, number of cumulative hours of headache-on-headache days, proportion of patients with severe HIT-6 score, and others). Injections of BoNT-A or placebo were injected as 31 fixed-sites, fixed-dose injections across 7 specific head/neck muscle areas. A discretionary 40 units could be administered using a “follow-the-pain” strategy, resulting in 195 units over 39 sites. Pooled analyses demonstrated a large mean decrease from baseline in frequency of headache days, with statistically significant between-group differences favoring onabotulinumtoxinA over placebo at week 24 (-8.4 vs. -6.6; $p < 0.001$) and at all other time points. Significant differences favoring onabotulinumtoxinA were also observed for all secondary efficacy variables at all time points, including frequency of headache days, cumulative headache hours, and the proportion of subjects with severe headaches. No significant difference was noted in the frequency of acute headache pain medication taken. There was a significantly greater proportion of experimental group subjects that had a greater that 50% decrease from baseline in headache days. Adverse events occurred in 62.4% of experimental group subjects and 51.7% of placebo subjects, with a greater than 5% incidence of neck pain and muscular weakness in the experimental group. The authors concluded that the use of onabotulinumtoxinA treatment for chronic migraine was effective, safe, and well tolerated.

Overactive Bladder

Nitti et al examined the efficacy and safety of onabotulinumtoxinA for the treatment of overactive bladder and urinary incontinence (UI) in a phase 3, randomized, multicenter, placebo-controlled trial. Adult patients (18 years or older) with idiopathic overactive bladder who experienced 3 or more urgency UI episodes in a 3-day period and an average of 8 or more micturitions per day were enrolled in the study. Patients were randomized 1:1 to either receive onabotulinumtoxinA 100 U or placebo over 20 evenly distributed intradetrusor injections. Co-primary end points were the change from baseline in the number of urinary incontinence episodes per day and the proportion of patients with a positive response on the treatment benefit scale at posttreatment week 12. Secondary end points included other overactive bladder symptoms and health related quality of life. OnabotulinumtoxinA significantly decreased the daily frequency of urinary incontinence episodes vs placebo (-2.65 vs -0.87, $p < 0.001$) and 22.9% vs 6.5% of patients became completely continent. A larger proportion of onabotulinumtoxinA than placebo treated patients reported a positive response on the treatment benefit scale (60.8% vs 29.2%, $p < 0.001$). All other overactive bladder symptoms improved vs placebo ($p < 0.05$). OnabotulinumtoxinA improved patient health related quality of life across multiple measures ($p < 0.001$). Uncomplicated urinary tract infection was the most common adverse event. A 5.4% rate of urinary retention was observed. The authors concluded that OnabotulinumtoxinA showed significant, clinically relevant improvement in all overactive bladder symptoms and health related quality of life in patients inadequately treated with anticholinergics and was well tolerated.

Spasticity (Associated With Cerebral Palsy)

In a global, randomized, placebo-controlled study, the efficacy and safety of abobotulinumtoxinA was evaluated for the treatment of spasticity in cerebral palsy children with dynamic equinus foot deformity. Two hundred and forty-one patients were randomized 1:1:1 to receive either abobotulinumtoxinA 10 U/kg/leg, 15 U/kg/leg, or placebo injections into the gastrocnemius-soleus complex of either one or both legs. The primary endpoint was the demonstration of benefit for each dose over placebo on the Modified Ashworth Scale from baseline to week 4. Secondary endpoint includes the change of the Physician’s Global Assessment at week 4 from baseline. Two hundred and twenty-six patients completed the study. At week 4, Modified Ashworth Scale scores significantly improved with abobotulinumtoxinA; mean (95% confidence interval) treatment differences versus placebo were -0.49 (-0.75 to -0.23; $p = 0.0002$) for 15 U/kg/leg and -0.38 (-0.64 to -0.13; p =

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0.003) for 10 U/kg/leg. The Physician's Global Assessment treatment differences versus placebo of 0.77 (0.45 to 1.10) for 15 U/kg/leg and 0.82 (0.50 to 1.14) for 10 U/kg/leg were also significant (both Ps < .0001). The most common treatment-related adverse event was muscular weakness (10 U/Kg/leg = 2; placebo = 1). The authors concluded that treatment with abobotulinumtoxinA improves muscle tone in children with dynamic equinus resulting in an improved overall clinical impression and is well tolerated.

An additional subgroup analysis was conducted on the same two-hundred and forty-one patients examined in the above study. Delgado et al. found that abobotulinumtoxin A was similarly effective in treating spasticity in cerebral palsy children with dynamic equinus foot deformity in both children who had not received botulinum toxin before and children who had previously received botulinum toxin. Of the 241 patients examined, 113 had received botulinum toxin treatment before participating in the study. Previous botulinum toxin treatment also had no effect on safety outcomes between the two groups.

Unproven

Benign Prostatic Hyperplasia

The efficacy and tolerability of botulinum toxin A (BoNT-A) for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia (LUTS/BPH) was evaluated in a randomized placebo-controlled trial involving 315 subjects assigned to either 200 U of BoNT-A (Botox) (n = 157) or placebo (n = 156). Patients with International Prostate Symptom Score (I-PSS) 14 or greater, with peak urinary flow rate 4 to 15 ml per second and total prostate volume 30 to 80 ml were randomized 1:1 to a single intraprostatic injection of BoNT-A or placebo. A single-blind sham procedure, followed by a 4-week run in was included to minimize potential placebo effect. The primary endpoint from baseline is total I-PSS at week 12. Additional endpoints assessed at weeks 6, 12, and 24 were peak urinary flow rate (Qmax), total prostate volume (TPV), and post-void residual urine volume (PVR). At all-time points there was no difference in I-PSS between the BoNT-A and placebo groups, included at the primary time point at 12 weeks, however both groups experienced a decrease (-6.3 vs -5.6 points, p < 0.001). There were no differences between treatment groups for TPV, PSA, or PVR at 12 or 24 weeks. The authors concluded that BoNT-A is unlikely to be a therapy for male LUTS/BPH.

In an additional phase III clinical trial completed in 2018, BoNT-A was tested against optimized oral medications in treating lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia. Four months after BoNT-A injection, most of the patients who received BoNT-A were able to interrupt LUTS-related medical treatments, but this study's design did not allow for a conclusion that this improvement was related to the study drug rather than a sustained placebo effect.

Chronic Daily Headache

Four studies were published in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders. Each of the studies specifically referenced chronic daily headache (CDH) and had a large population of patients with transformed migraine. The primary outcome measure for all the studies was mean change in headache-free days per month. The first study, which used a technique of modifying injection site based on location of pain, showed a significant benefit (11 days vs. 8 days) in the BoNTA treated population. The second study, the largest of patients with CDH, was a randomized, double-blind, placebo-controlled, phase II study, enrolling 702 patients. This trial used a fixed-site strategy. Eligible patients were injected with BoNTA at 225 U, 150 U, 75 U, or placebo and returned for additional masked treatments at day 90 and day 180. Patients were assessed every 30 days for 9 months. The primary efficacy end point was the mean change from baseline in the frequency of headache-free days at day 180 for the placebo nonresponder group. The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed with BoNTA at 225 U, 150 U, 75 U, or placebo, respectively (p = 0.44). However, a priori-defined analysis of headache change from baseline in headache frequency revealed that the 225 U and 150 U Botox A groups had statistically significant greater reductions in headache frequency compared with placebo at day 240 (p = 0.03). In conclusion, BoNTA was safe and well tolerated. Although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240, but the placebo response was higher than expected. The third study was a subgroup of patients not taking prophylactic medications from a larger overall study. Only this subgroup showed a significant mean increase in headache-free days although there was a decrease in the frequency per 30 days. An additional study evaluated 82 patients with chronic daily headache treated with botulinum neurotoxin A. 76.1% of the chronic migraine patients and 36.4% of the chronic tension-type headache patients were considered responders. Because studies of botulinum A for the prevention of chronic daily headache show mixed results, further studies are recommended.

Tension Headache

Four studies of patients with tension-type headache were reviewed in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders. Patients in these studies were randomized to either botulinum neurotoxin (BoNT) or placebo. After 6 weeks, the first study (n = 112) showed no significant difference compared to a

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baseline 6-week period in the primary outcome measure of area under the headache curve in the subjects' headache diary. In another of the studies, both the BoNT and the placebo group showed improvement in the primary outcome of mean change from baseline in number of headache-free days from 30 to 60 after injection, but BoNT was not more beneficial, and a power analysis was not provided. A third study showed no significant benefit of BoNT after 12 weeks for decrease of headache, intensity on visual analog scale, mean number of headache days, headache hours per day, days on which symptomatic treatment was taken, number of analgesics taken per day, or patient's assessment of improvement. The fourth study, a smaller trial, included 16 patients in a prospective double-blind, placebo-controlled crossover study and thirty patients in an open-label long-term study. These patients showed reduction in headache severity and pericranial muscle tenderness, and increased headache-free days with botulinum treatment.

Additional small randomized controlled trials have found conflicting results similar to those presented above. Until larger randomized trials are conducting showing a beneficial effect of BTX-A, its use in tension headache is unproven.

Miscellaneous

Botulinum toxin A has been studied in a number of other disorders including: cricopharyngeal dysphagia, gustatory epiphora (crocodile tears), Sphincter of Oddi dysfunction, pancreas divisum, anismus, lower urinary tract dysfunction, pelvic floor spasticity, chronic prostatic pain, severe paradoxical vocal cord movement, post-parotidectomy sialoceles, severe bruxism, temporomandibular disorders, myofascial pain syndrome, brachial plexus palsy, thyroid associated ophthalmopathy, esophageal spasm, post-thoracotomy pseudoangina, epiphora following salivary gland transplantation, trigeminal neuralgia, trismus and stridor in amyotrophic lateral sclerosis, proctalgia fugax, nasal hypersecretion, gastroparesis (including diabetic gastroparesis), Lichen simplex, lateral epicondylitis, Stiff-person syndrome, traumatic sixth nerve palsy, Tourette's syndrome, chronic scrotal pain, and pain and/or wound healing after hemorrhoidectomy. The studies in these disorders have been small and/or uncontrolled open-label trials. Larger, well-designed studies must occur to demonstrate the effectiveness of botulinum toxin in the treatment of these conditions.

Technology Assessments

Achalasia

A 2014 Cochrane review was published evaluating and comparing endoscopic pneumatic dilation (PD) versus botulinum toxin injection in the management of primary achalasia. Seven studies involving 178 participants were included. Two studies were excluded from the meta-analysis of remission rates on the basis of clinical heterogeneity of the initial endoscopic protocols. There was no significant difference between PD or botulinum treatment in remission within four weeks of the initial intervention; with a risk ratio of remission of 1.11 (95% CI 0.97 to 1.27). There was also no significant difference in the mean esophageal pressures between the treatment groups; with a weighted mean difference for PD of -0.77 (95% CI -2.44 to 0.91, p = 0.37). Data on remission rates following the initial endoscopic treatment were available for three studies at six months and four studies at 12 months. At six months 46 of 57 PD participants were in remission compared to 29 of 56 in the botulinum group, giving a risk ratio of 1.57 (95% CI 1.19 to 2.08, p = 0.0015); whilst at 12 months 55 of 75 PD participants were in remission compared to 27 of 72 botulinum participants, with a risk ratio of 1.88 (95% CI 1.35 to 2.61, p = 0.0002). No serious adverse outcomes occurred in participants receiving botulinum, while PD was complicated by perforation in three cases. The authors concluded that PD is the more effective endoscopic treatment in the long term (greater than six months) for patients with achalasia.

Cervical Dystonia

A 2020 Cochrane systematic review evaluated the efficacy and safety of botulinum toxin type A (BtA) for cervical dystonia. The review included nine randomized controlled trials involving 1,144 participants. Compared with placebo, BtA resulted in clinically meaningful improvements in cervical dystonia severity, disability, and pain, with an average 8.09-point improvement in TWSTRS total score at four weeks. Both clinicians and patients were more likely to report overall improvement with BtA treatment.

BtA treatment was associated with an increased risk of adverse events, most commonly dysphagia, neck weakness, and diffuse weakness or tiredness. However, participants receiving BtA were less likely to discontinue treatment overall. The review found no clear evidence of a dose-response relationship, superiority among BtA formulations, or additional benefit from electromyography-guided injections. The authors concluded that there is moderate-certainty evidence that a single BtA treatment session provides clinically meaningful improvement in cervical dystonia and pain and is generally well tolerated, although evidence regarding long-term treatment outcomes remains limited

Chronic and Episodic Migraine Headache

A 2018 Cochrane review was published evaluating the effects of botulinum toxins versus placebo or active treatment for the prevention or reduction in frequency of chronic or episodic migraine in adults. Twenty-eight studies, involving 4,190

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participants, were eligible for inclusion. The longest treatment duration was three rounds of injections with three months between treatments, so the authors could not analyze long-term effects. For the primary analyses, the authors pooled data from both chronic and episodic participant populations. Where possible, the authors also separated data into chronic migraine, episodic migraine and 'mixed group' classification subgroups. Most trials (21 out of 28) were small (fewer than 50 participants per trial arm). The risk of bias for included trials was low or unclear across most domains, with some trials reporting a high risk of bias for incomplete outcome data and selective outcome reporting. Twenty-three trials compared botulinum toxin with placebo. Botulinum toxin may reduce the number of migraine days per month in the chronic migraine population by 3.1 days [95% confidence interval (CI) -4.7 to -1.4, 4 trials, 1497 participants, low-quality evidence]. This was reduced to -2 days (95% CI -2.8 to -1.1, 2 trials, 1384 participants; moderate-quality evidence) when the authors removed small trials. A single trial of people with episodic migraine (n = 418) showed no difference between groups for this outcome measure (p = 0.49).In the chronic migraine population, botulinum toxin reduces the number of headache days per month by 1.9 days (95% CI -2.7 to -1.0, 2 trials, 1384 participants, high-quality evidence). The authors did not find evidence of a difference in the number of migraine attacks for both chronic and episodic migraine participants (6 trials, n = 2004, p = 0.30, low-quality evidence). For the population of both chronic and episodic migraine participants, a reduction in severity of migraine rated during clinical visits, on a 10 cm visual analog scale (VAS) of 3.3 cm (95% CI -4.2 to -2.5, very low-quality evidence) in favor of botulinum toxin treatment came from four small trials (n = 209); better reporting of this outcome measure from the additional eight trials that recorded it may have improved our confidence in the pooled estimate. Global assessment and quality-of-life measures were poorly reported, and it was not possible to carry out statistical analysis of these outcome measures. Analysis of adverse events showed an increase in the risk ratio with treatment with botulinum toxin over placebo 30% (RR 1.28, 95% CI 1.12 to 1.47, moderate-quality evidence). For every 100 participants, 60 experienced an adverse event in the botulinum toxin group compared with 47 in the placebo group. Three trials studied comparisons with alternative oral prophylactic medications. Meta-analyses were not possible for number of migraine days, number of headache days or number of migraine attacks due to insufficient data, but individually trials reported no differences between groups for a variety of efficacy measures in the population of both chronic and episodic migraine participants. The global impression of disease measured using Migraine Disability Assessment (MIDAS) scores were reported from two trials that showed no difference between groups. Compared with oral treatments, botulinum toxin showed no between-group difference in the risk of adverse events (2 trials, n = 114, very low-quality evidence). The relative risk reduction (RRR) for withdrawing from botulinum toxin due to adverse events compared with the alternative prophylactic agent was 72% (p = 0.02, 2 trials, n = 119). There were insufficient data available for the comparison of different doses. The quality of the evidence assessed using GRADE methods was varied but mostly very low; the quality of the evidence for the placebo and active control comparisons was low and very low, respectively for the primary outcome measure. Small trial size, high risk of bias and unexplained heterogeneity were common reasons for downgrading the quality of the evidence. The authors concluded that for chronic migraine, botulinum toxin type A may reduce the number of migraine days per month by 2 days compared with placebo treatment. Non-serious adverse events were probably experienced by 60/100 participants in the treated group compared with 47/100 in the placebo group. For people with episodic migraine, the authors remain uncertain whether or not this treatment is effective because the quality of this limited evidence is very low. Better reporting of outcome measures in published trials would provide a more complete evidence base on which to draw conclusions.

Strabismus

A 2017 update to a 2012 Cochrane review was published to examine the efficacy of botulinum toxin therapy in the treatment of strabismus compared with alternative conservative or surgical treatment options. The review also sought to determine the types of strabismus that particular benefit from the use of botulinum toxin as a treatment option. The secondary objectives were to investigate the dose effect and complication rates associated with botulinum therapy. Six randomized controlled trials were eligible for inclusion. The authors concluded that the published literature on the use of botulinum toxin in the treatment of strabismus consists of retrospective studies, cohort studies or case reviews. These provide useful descriptive information; clarification is required as to the effective use of botulinum toxin as an independent treatment modality. Six RCTs on the therapeutic use of botulinum toxin in strabismus, graded as low and very low-certainty evidence, have shown varying responses. These include a lack of evidence for effect of botulinum toxin on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and botulinum toxin are combined. Further high-quality trials using robust methodologies are required to compare the clinical and cost effectiveness of various forms of botulinum toxin (e.g., Dysport, Xeomin, etc.), to compare botulinum toxin with and without adjuvant solutions and to compare botulinum toxin to alternative surgical interventions in strabismus cases with and without potential for binocular vision.

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Motor/Phonic Tics

A 2018 Cochrane review was published evaluating the safety and effectiveness of botulinum toxin in treating motor and phonic tics in people with Tourette's syndrome, and to analyze the effect of botulinum toxin on premonitory urge and sensory tics. Only one randomized placebo-controlled, double-blind cross-over study met our selection criteria. In this study, 20 participants with motor tics were enrolled over a three-year recruitment period; 18 (14 of whom had a diagnosis of Tourette's syndrome) completed the study; in total, 21 focal motor tics were treated. Although we considered most bias domains to be at low risk of bias, the study recruited a small number of participants with relatively mild tics and provided limited data for our key outcomes. The effects of botulinum toxin injections on tic frequency, measured by videotape or rated subjectively, and on premonitory urge, are uncertain (very low-quality evidence). The quality of evidence for adverse events following botulinum toxin was very low. Nine people had muscle weakness following the injection, which could have led to unblinding of treatment group assignment. No data were available to evaluate whether botulinum injections led to immunoresistance to botulinum. The authors concluded that they are uncertain about botulinum toxin effects in the treatment of focal motor and phonic tics in select cases, as we assessed the quality of the evidence as very low. Additional randomized controlled studies are needed to demonstrate the benefits and harms of botulinum toxin therapy for the treatment of motor and phonic tics in patients with Tourette's syndrome.

Professional Societies

Neurogenic Lower Urinary Tract Dysfunction

In 2021, the American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine & Reconstructive Surgery (SUFU) published a guideline on the management of adults with neurogenic lower urinary tract dysfunction (NLUTD).

Recommendations regarding botulinum toxin therapy include:

- In NLUTD patients with spinal cord injury or multiple sclerosis who are refractory to oral medications, clinicians should recommend onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve quality of life (Strong Recommendation; Evidence Level: Grade A).
- In NLUTD patients, other than those with spinal cord injury or multiple sclerosis, who are refractory to oral medications, clinicians may offer onabotulinumtoxinA to improve bladder storage parameters, decrease episodes of incontinence, and improve quality of life (Conditional Recommendation; Evidence Level: Grade C).
- In NLUTD patients who spontaneously void, clinicians should discuss the risk of urinary retention and the potential need for intermittent catheterization prior to treatment with botulinum toxin (Clinical Principle).

The guideline concluded that onabotulinumtoxinA improves urinary incontinence, bladder storage function, and quality of life in appropriately selected adults with neurogenic detrusor overactivity, with the strongest evidence in patients with spinal cord injury and multiple sclerosis.

Spasmodic Dysphonia (Laryngeal Dystonia)

In 2018, the American Academy of Otolaryngology – Head and Neck Surgery published an update of their guideline first published in 2009. The organization recommended that clinicians should offer, or refer to a clinician who can offer botulinum toxin injections for the treatment of dysphonia caused by spasmodic dysphonia and other types of laryngeal dystonia.

A recommendation means that the benefits exceed the harms (or that the harms exceed the benefits, in the case of a negative recommendation) but that the quality of evidence is not as strong (grade B or C). In some clearly identified circumstances, recommendations may be made on the basis of lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.

Achalasia

In 2020, the American College of Gastroenterology published an evidence-based clinical guideline for the diagnosis and management of achalasia based on a comprehensive review of the pertinent evidence and examination of relevant published data. The recommendations for the treatment of achalasia from this guideline are as follows:

- In patients with achalasia who are candidates for definite therapy:
  - Pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), and peroral endoscopic myotomy (POEM) are comparable effective therapies for type I or type II achalasia.
  - POEM would be a better treatment option in those with type III achalasia.
  - Botulinum toxin injection is reserved for those who cannot undergo the above definitive therapies.

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- Recommend botulinum toxin injection as first-line therapy for patients with achalasia who are unfit for definitive therapies compared with other less effective pharmacological therapies (Grade quality: Moderate; Recommendation strength: Strong).
- Previous treatment with botulinum toxin injection does not significantly affect performance and outcomes of myotomy (Grade quality: Low; Recommendation strength: Conditional).

Autonomic & Movement Disorders, Pain, and Spasticity

In a 2013 update to the 2008 Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U) assessments on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain, movement disorders, and spasticity. In addition, in 2013 authors performed an assessment on the use of botulinum neurotoxin in the treatment of urologic conditions and secretory disorders based on the AAN methodology. The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society also published an evidence-based review of the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy in 2010.

Recommendations from these reviews are classified as follows:

- Level A - Established as effective, ineffective, or harmful for the given condition in the specified population, requiring at least two consistent Class I studies.
- Level B - Probably effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class I study or at least two consistent Class II studies.
- Level C - Possibly effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class II study or two consistent Class III studies.
- Level U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Recommendations from these reviews are:

- BoNT should be offered as a treatment option for axillary hyperhidrosis and detrusor overactivity (detrusor hyperreflexia) (Level A). BoNT should be considered for palmar hyperhidrosis, sialorrhea, and detrusor sphincter dyssynergia after spinal cord injury (Level B).
- BoNT is probably effective for the treatment of benign prostatic hyperplasia induced lower urinary tract symptoms (Level B).
- BoNT may be considered for low back pain (Level C). BoNT is probably ineffective in episodic migraine and chronic tension-type headache (Level B).
- Evidence does not permit drawing conclusions on BoNT's efficacy in chronic daily headache (mainly transformed migraine) (Level U). Evidence does not support BoNT's efficacy for the treatment of gustatory sweating (Level U).
- BoNT should be offered as an option for the treatment of blepharospasm, cervical dystonia (Level A).
- BoNT may be offered for, hemifacial spasm, focal upper extremity dystonia, and upper extremity essential tremor (Level B).
- BoNT may be considered for, adductor laryngeal dystonia, focal lower limb dystonia, oromandibular dystonia, and motor tics (Level C).
- BoNT should be offered as an option for the treatment of spasticity in adults (Level A). Spasticity in adults results from a variety of causes such as stroke, trauma, multiple sclerosis, and neoplasm involving the central nervous system.
- For localized/segmental spasticity that warrants treatment in children and adolescents with cerebral palsy, botulinum toxin type A should be offered as an effective and generally safe treatment (Level A) and there is insufficient data to support or refute the use of botulinum toxin type B (Level U).

Tics in People With Tourette's Syndrome and Chronic Tic Disorder

In 2019, the American Academy of Neurology (AAN) published evidence-based guideline recommendations regarding the use of botulinum neurotoxins in treating tics in people with Tourette's Syndrome, as well as treating chronic tic disorder (studies classified as Class I to IV and recommendations classified as levels A to C). The recommendations for the treatment of tics in people with Tourette's Syndrome and chronic tic disorder from this guideline are as follows:

- Physicians may prescribe botulinum toxin injections for the treatment of older adolescents and adults with localized and bothersome simple motor tics when the benefits of treatment outweigh the risks (Level C).
- Physicians may prescribe botulinum toxin injections for the treatment of older adolescents and adults with severely disabling or aggressive vocal tics when the benefits of treatment outweigh the risks (Level C).
- Physicians must counsel individuals with tics that botulinum toxin injections may cause weakness and hypophonia, and that all effects are temporary (Level A).

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Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache

In a 2016 update to the 2008 guidelines, the American Academy of Neurology (AAN) published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U) assessments on the use of botulinum neurotoxins in the treatment of blepharospasm, cervical dystonia, headache, and adult spasticity.

Recommendations from this review are classified as follows:

- Level A - Established as effective, ineffective, or harmful for the given condition in the specified population, requiring at least two consistent Class I studies.
- Level B - Probably effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class I study or at least two consistent Class II studies.
- Level C - Possibly effective, ineffective, or harmful for the given condition in the specified population, requiring at least one Class II study or two consistent Class III studies.
- Level U - Data inadequate or conflicting; given current knowledge, treatment is unproven.

Recommendations from this review for abobotulinumtoxinA (aboBoNT-A, Dysport) are as follows:

- AboBoNT-A should be offered as a treatment option for cervical dystonia, focal manifestations of upper limb spasticity, and focal manifestations of lower limb spasticity that warrant treatment (Level A).
  - AboBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies). AboBoNT-A has also been established as safe and effective for the reduction of adult lower limb spasticity (multiple Class I studies).
  - Data is inadequate to determine the efficacy of aboBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes). Data is also inadequate to determine the efficacy of aboBoNT-A for improvement of active function associated with adult lower limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple Class I studies).
- AboBoNT-A may be considered as a treatment option for blepharospasm (Level C).

Recommendations from this review for incobotulinumtoxinA (incoBoNT-A, Xeomin) are as follows:

- IncoBoNT-A should be offered as a treatment option for focal manifestations of upper limb spasticity (Level A).
  - IncoBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies).
  - Data is inadequate to determine the efficacy of incoBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes).
- IncoBoNT-A should be considered as a treatment option for blepharospasm and cervical dystonia (Level B).
- There is insufficient evidence to support or refute the use of incoBoNT-A for the treatment of lower limb spasticity (Level U).

Recommendations from this review for onabotulinumtoxinA (onaBoNT-A, Botox) are as follows:

- OnaBoNT-A should be offered as a treatment option for focal manifestations of upper limb spasticity, focal manifestations of lower limb spasticity that warrant treatment, and chronic migraine (Level A).
  - OnaBoNT-A has been established as safe and effective for the reduction of adult upper limb spasticity and improvement of passive function (multiple Class I studies). OnaBoNT-A has also been established as safe and effective for the reduction of adult lower limb spasticity (multiple Class I studies).
  - Data is inadequate to determine the efficacy of onaBoNT-A for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes). Data is also inadequate to determine the efficacy of onaBoNT-A for improvement of active function associated with adult lower limb spasticity (no studies available or inconsistent results dependent on specific outcome from multiple Class I studies).
- OnaBoNT-A should be considered as a treatment option for blepharospasm and cervical dystonia (Level B).
- OnaBoNT-A should not be offered as a treatment option for episodic migraine (Level A).
- OnaBoNT-A should not be considered as a treatment option for tension-type headache (Level B).

Recommendations from this review for rimabotulinumtoxinB (rimaBoNT-B, Myobloc) are as follows:

- RimaBoNT-B should be offered as a treatment option for cervical dystonia (Level A).
- RimaBoNT-B should be considered as a treatment option for focal manifestations of upper limb spasticity (Level B).
  - RimaBoNT-B is probably safe and effective for the reduction of adult upper limb spasticity (1 Class I study).
  - Data is inadequate to determine the efficacy of rimaBoNT-B for improvement of active function associated with adult upper limb spasticity (Class I studies, inconsistent results dependent on active functional outcomes).

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- There is insufficient evidence to support or refute the use of rimaBoNT-B for the treatment of blepharospasm and lower limb spasticity (Level U).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

For non-cosmetic use, abobotulinumtoxinA (Dysport) is FDA-approved for the treatment of adults with cervical dystonia. Dysport is also indicated for the treatment of spasticity in pediatric patients 2 years of age and older.

IncobotulinumtoxinA (Xeomin) is FDA-approved for the treatment of adults with cervical dystonia. Xeomin is also indicated for the treatment of adults with blepharospasm, upper limb spasticity in patients 2 years of age and older , and chronic sialorrhea in patients 2 years of age and older.

For non-cosmetic use, daxibotulinumtoxinA-lanm (Daxxify) is FDA-approved for the treatment of cervical dystonia in adult patients.

For non-cosmetic use, onabotulinumtoxinA (Botox) is FDA-approved for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer). Safety and effectiveness of Botox have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month).

Botox is also approved for treatment of spasticity in patients 2 years of age and older.

Botox is also indicated for reducing the severity of abnormal head position and neck pain associated with cervical dystonia in adults; for the treatment of strabismus and blepharospasm associated with dystonia; for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response or are intolerant to an anticholinergic medication; for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication; 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; and for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. Safety and efficacy of Botox for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive Botox for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease. Safety and effectiveness of Botox have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

RimabotulinumtoxinB (Myobloc) is FDA-approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. It is also FDA-approved for the treatment of chronic sialorrhea in adults.

All botulinum toxin products approved by the FDA carry a black box warning regarding the possibility of the distant spread of toxin effect. The warning states that post marketing reports indicate that the effects of all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and upper limb spasticity and at lower doses.

Centers for Medicare and Medicaid Services (CMS)

Coverage guidelines for certain Part B drugs may be found in the Medicare Advantage Medical Policy titled Medications/Drugs (Outpatient/Part B). National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. These NCDs/LCDs/LCAs are available at https://www.cms.gov/medicare-coverage-database/new-search/search.aspx.

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In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that certain criteria are met, including that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

*Preferred therapy criteria for Medicare Advantage members, refer to Medicare Part B Step Therapy Programs.

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Policy History/Revision Information

Date	Summary of Changes
11/01/2026	**Applicable Codes** • Updated list of applicable ICD-10 diagnosis codes for HCPCS codes J0585 and J0586; added H49.00, H49.01, H49.02, H49.03, H49.10, H49.11, H49.12, H49.13, H49.20, H49.21, H49.22, H49.23, H49.30, H49.31, H49.32, H49.33, H49.40, H49.41, H49.42, H49.43, H49.811, H49.812, H49.813, H50.00, H50.011, H50.012, H50.021, H50.022, H50.031, H50.032, H50.041, H50.042, H50.05, H50.06, H50.07, H50.08, H50.10, H50.111, H50.112, H50.121, H50.122, H50.131, H50.132, H50.141, H50.142, H50.15, H50.16, H50.17, H50.18, H50.30, H50.311, H50.312, H50.32, H50.331, H50.332, H50.34, H50.40, H50.411, H50.412, H50.42, H50.43, H50.50, H50.51, H50.52, H50.53, H50.54, H50.55, H50.611, H50.612, H50.621, H50.622, H50.629, H50.631, H50.632, H50.639, H50.641, H50.642, H50.649, H50.651, H50.652, H50.659, H50.661, H50.662, H50.669, H50.671, H50.672, H50.679, H50.681, H50.682, H50.689, H50.811, and H50.812 **Supporting Information** • Updated *Clinical Evidence*, *FDA*, *CMS*, and *References* sections to reflect the most current information • Archived previous policy version 2026D0017AN

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its policies and guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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