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MEDICAL POLICY – 5.01.512

Botulinum Toxins

Effective Date:	May 1, 2024	RELATED MEDICAL POLICIES:	
Last Revised:	April 22, 2024	2.01.535	Temporomandibular Joint Disorder
Replaces:	N/A	8.01.519	Nonpharmacologic Treatment of Hyperhidrosis
		10.01.514	Cosmetic and Reconstructive Services

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POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | APPENDIX | HISTORY

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Introduction

The botulinum toxin is a protein that is produced by the bacterium Clostridium botulinum. The botulinum toxin acts on the nervous system. It blocks the release of a chemical messenger (acetylocholine) that causes muscles to contract. When the botulinum toxin is injected in small doses, it relaxes muscles. It can be used for several medical conditions, including: abnormal muscle stiffness, chronic migraine, certain facial nerve disorders, excessive drooling, misaligned eyes, overactive bladder, severe neck/shoulder muscle contractions, tears in the lining of the anus, and uncontrollable blinking. Botulinum toxin can also be used for problems with muscle movement in certain diseases of the central nervous system. Several forms of the botulinum toxin are available. Each has its own specific uses and dosing guidelines. This policy describes when botulinum toxin may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Botox (onabotulinumtoxinA)	**Botox (onabotulinumtoxinA) may be considered medically necessary for the prophylaxis of chronic migraine headaches when the following criteria are met:** • Individual is 18 years of age or older **AND** • Has an average of 15 or more headache days per month where headaches last ≥ 4 hours per day **AND** • Tried two different categories of prophylactic migraine headache therapies listed in the **Appendix** section for at least 8 weeks each **Botox (onabotulinumtoxinA) may be considered medically necessary for the treatment of overactive bladder (OAB) when the following criteria are met:** • Individual is 18 years of age or older **AND** • Tried ≥ 2 anticholinergic medications (e.g., darifenacin, oxybutynin, tolterodine, trospium, solifenacin) first and had an inadequate response or intolerance to both anticholinergic medications **Botox (onabotulinumtoxinA) may be considered medically necessary for the treatment of urinary incontinence due to detrusor overactivity when the following criteria are met:** • Individual is 18 years of age or older **AND** • The urinary incontinence is due to a neurologic condition (e.g., spinal cord injury, multiple sclerosis) **AND** • Tried ≥ 2 anticholinergic medications (e.g., darifenacin, oxybutynin, tolterodine, trospium, solifenacin) first and had an inadequate response or intolerance to both anticholinergic medications

Drug	Medical Necessity
	Botox (onabotulinumtoxinA) may be considered medically necessary for the treatment of neurogenic detrusor overactivity (NDO) in pediatric individuals when the following criteria are met: • Individual is 5 to 17 years of age **AND** • The urinary incontinence due to detrusor overactivity is associated with a neurologic condition (e.g., spina bifida, spinal cord injury, transverse myelitis) **AND** • Tried ≥ 1 anticholinergic medication (e.g., darifenacin, oxybutynin, tolterodine, trospium, solifenacin) first and had an inadequate response or intolerance to the anticholinergic medication **Botox (onabotulinumtoxinA) may be considered medically necessary for the treatment of cervical dystonia (also called spasmodic torticollis) when the following criteria are met:** • Individual is 18 years of age or older **AND** • There is a sustained head tilt or abnormal posturing with limited range of motion in the neck **AND** • History of recurrent involuntary contraction of 1 or more of the muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles) **AND** • Individual does not have acute cervical dystonia caused by exposure to dopamine receptor-blocking drugs (e.g., antipsychotics, lithium, metoclopramide, etc.) **Botox (onabotulinumtoxinA) may be considered medically necessary for the treatment of adults with primary focal axillary or palmar hyperhidrosis when the following criteria are met:** • For the treatment of a functional impairment* as seen in any of the following medical conditions:

Drug	Medical Necessity
	○ Acrocyanosis (bluish discoloration) of the hands; **or** ○ History of recurrent skin maceration with bacterial or fungal infections; **or** ○ History of recurrent secondary infections; **or** ○ History of persistent eczematous dermatitis despite medical treatments with topical dermatologic or systemic anticholinergic agents **AND** • Individual is ≥ 18 years of age **AND** • Axillary or palmer hyperhidrosis has been inadequately managed with topical agents (e.g., OTC aluminum chloride antiperspirant, glycopyrronium tosylate wipes) ***Note**: See **Definition of Terms** below **Botox (onabotulinumtoxinA) may be considered medically necessary for the treatment of adults with dystonia resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in individuals with any of the following:** • Focal upper-limb dystonia (e.g., organic writer's cramp) • Idiopathic (primary or genetic) torsion dystonia • Laryngeal dystonia (adductor spasmodic dysphonia) • Oromandibular dystonia (orofacial dyskinesia, Meige syndrome) • Symptomatic (acquired) torsion dystonia **Botox (onabotulinumtoxinA) may also be considered medically necessary for the treatment of:** • Blepharospasm associated with dystonia, including benign essential blepharospasm or facial nerve (VII) disorders, in individuals 12 years of age and older • Chronic anal fissure in individuals who had an inadequate response or intolerance to 1 of the following conventional

Drug	Medical Necessity
	therapies: topical nitrates or topical calcium channel blockers (e.g., diltiazem, nifedipine) • Esophageal achalasia in individuals who have not responded to dilation therapy or who either are considered poor surgical candidates or require treatment before surgery can be done • Hemifacial spasms in individuals 18 years of age and older • Hirschsprung disease in individuals who develop obstructive symptoms after a pull-through operation • Lower limb and upper limb spasticity in individuals 2 years of age and older • Strabismus in individuals 12 years of age and older **Note:** The use of Botox (onabotulinumtoxinA) is considered not medically necessary as a treatment of wrinkles or any other cosmetic indications.
Daxxify (daxibotulinumtoxinA-lanm)	**Daxxify (daxibotulinumtoxinA-lanm) may be considered medically necessary for the treatment of cervical dystonia (also called spasmodic torticollis) when the following criteria are met:** • Individual is 18 years of age or older **AND** • There is a sustained head tilt or abnormal posturing with limited range of motion in the neck **AND** • History of recurrent involuntary contraction of 1 or more of the muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles) **AND** • Individual does not have acute cervical dystonia caused by exposure to dopamine receptor-blocking drugs (e.g., antipsychotics, lithium, metoclopramide, etc.) **Note**: The use of Daxxify (daxibotulinumtoxinA-lanm) is considered not medically necessary as a treatment of wrinkles or any other cosmetic indications.

Drug	Medical Necessity
Dysport (abobotulinumtoxinA)	**Dysport (abobotulinumtoxinA) may be considered medically necessary for the treatment of cervical dystonia (also called spasmodic torticollis) when the following criteria are met:** • Individual is 18 years of age or older **AND** • There is a sustained head tilt or abnormal posturing with limited range of motion in the neck **AND** • History of recurrent involuntary contraction of 1 or more of the muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles) **AND** • Individual does not have acute cervical dystonia caused by exposure to dopamine receptor-blocking drugs (e.g., antipsychotics, lithium, metoclopramide, etc.) **Dysport (abobotulinumtoxinA) may be considered medically necessary for the treatment of adults with dystonia resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in individuals with any of the following:** • Focal upper-limb dystonia (e.g., organic writer's cramp) • Idiopathic (primary or genetic) torsion dystonia • Laryngeal dystonia (adductor spasmodic dysphonia) • Oromandibular dystonia (orofacial dyskinesia, Meige syndrome) • Symptomatic (acquired) torsion dystonia **Dysport (abobotulinumtoxinA) may also be considered medically necessary for the treatment of:** • Chronic anal fissure in individuals who had an inadequate response or intolerance to 1 of the following conventional therapies: topical nitrates or topical calcium channel blockers (e.g., diltiazem, nifedipine) • Esophageal achalasia in individuals who have not responded to dilation therapy or who are either considered poor surgical candidates or require treatment before surgery can be done

Drug	Medical Necessity
	• Hemifacial spasms in individuals 18 years of age and older • Hirschsprung disease in individuals who develop obstructive symptoms after a pull-through operation • Lower limb and upper limb spasticity in individuals 2 years of age and older **Note:** The use of Dysport (abobotulinumtoxinA) is considered not medically necessary as a treatment of wrinkles or any other cosmetic indications.
Jeuveau (prabotulinumtoxinA-xvfs)	**Jeuveau (prabotulinumtoxinA-xvfs) is cosmetic for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult individuals.** **Note**: Jeuveau is FDA-approved for cosmetic use for this indication only. This use is cosmetic and is not covered.
Letybo (letibotulinumtoxinA-wlbg)	**Letybo (letibotulinumtoxinA-wlbg) is cosmetic for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult individuals.** **Note**: Letybo is FDA-approved for cosmetic use for this indication only. This use is cosmetic and is not covered.
Myobloc (rimabotulinumtoxinB)	**Myobloc (rimabotulinumtoxinB) may be considered medically necessary for the treatment of cervical dystonia (also called spasmodic torticollis) when the following criteria are met:** • Individual is 18 years of age or older **AND** • There is a sustained head tilt or abnormal posturing with limited range of motion in the neck **AND** • History of recurrent involuntary contraction of 1 or more of the muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles) **AND**

Drug	Medical Necessity
	• Individual does not have acute cervical dystonia caused by exposure to dopamine receptor-blocking drugs (e.g., antipsychotics, lithium, metoclopramide, etc.) **Myobloc (rimabotulinumtoxinB) may be considered medically necessary for the treatment of adults with dystonia resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in individuals with any of the following:** • Focal upper-limb dystonia (e.g., organic writer's cramp) • Idiopathic (primary or genetic) torsion dystonia • Laryngeal dystonia (adductor spasmodic dysphonia) • Oromandibular dystonia (orofacial dyskinesia, Meige syndrome) • Symptomatic (acquired) torsion dystonia **Myobloc (rimabotulinumtoxinB) may also be considered medically necessary for the treatment of chronic sialorrhea in adult individuals who have tried ≥ 1 oral agent (e.g., glycopyrrolate, benztropine) first and had an inadequate response or intolerance to the medication.** **Myobloc (rimabotulinumtoxinB) may also be considered medically necessary for the treatment of:** • Hemifacial spasms in individuals 18 years of age and older **Note:** The use of Myobloc (rimabotulinumtoxinB) is considered not medically necessary as a treatment of wrinkles or any other cosmetic indications.
Xeomin (incobotulinumtoxinA)	**Xeomin (incobotulinumtoxinA) may be considered medically necessary for the treatment of upper limb spasticity in pediatric individuals when the following criteria are met:** • Individual is 2 to 17 years of age **AND** • The spasticity is NOT caused by cerebral palsy

Drug	Medical Necessity
	Xeomin (incobotulinumtoxinA) may be considered medically necessary for the treatment of cervical dystonia (also called spasmodic torticollis) when the following criteria are met: • Individual is 18 years of age or older **AND** • There is a sustained head tilt or abnormal posturing with limited range of motion in the neck **AND** • History of recurrent involuntary contraction of 1 or more of the muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, or posterior cervical muscles) **AND** • Individual does not have acute cervical dystonia caused by exposure to dopamine receptor-blocking drugs (e.g., antipsychotics, lithium, metoclopramide, etc.) **Xeomin (incobotulinumtoxinA) may be considered medically necessary for the treatment of adults with dystonia resulting in functional impairment (interference with joint function, mobility, communication, nutritional intake) and/or pain in individuals with any of the following:** • Focal upper-limb dystonia (e.g., organic writer's cramp) • Idiopathic (primary or genetic) torsion dystonia • Laryngeal dystonia (adductor spasmodic dysphonia) • Oromandibular dystonia (orofacial dyskinesia, Meige syndrome) • Symptomatic (acquired) torsion dystonia **Xeomin (incobotulinumtoxinA) may also be considered medically necessary for the treatment of:** • Blepharospasm in individuals 18 years of age and older • Chronic anal fissure in individuals who had an inadequate response or intolerance to 1 of the following conventional therapies: topical nitrates or topical calcium channel blockers (e.g., diltiazem, nifedipine) • Chronic sialorrhea in individuals 2 years of age and older who have tried ≥1 oral agent (e.g., glycopyrrolate, benztropine) first

Drug	Medical Necessity
	and had an inadequate response or intolerance to the medication • Esophageal achalasia in individuals who have not responded to dilation therapy or who are either considered poor surgical candidates or require treatment before surgery can be done • Hemifacial spasms in individuals 18 years of age and older • Hirschsprung disease in individuals who develop obstructive symptoms after a pull-through operation • Upper limb spasticity in adults **Note:** The use of Xeomin (incobotulinumtoxinA) is considered not medically necessary as a treatment of wrinkles or any other cosmetic indications.

Drug	Investigational

• **Botox (onabotulinumtoxinA),**
• **Daxxify (daxibotulinumtoxinA-lanm),**
• **Dysport (abobotulinumtoxinA),**
• **Jeuveau (prabotulinumtoxinA-xvfs),**
• **Letybo (letibotulinumtoxinA-wlbg),**
• **Myobloc (rimabotulinumtoxinB),**
• **Xeomin (incobotulinumtoxinA)**
	The use of Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Daxxify (daxibotulinumtoxinA-lanm), Jeuveau (prabotulinumtoxinA-xvfs), Letybo (letibotulinumtoxinA-wlbg), Myobloc (rimabotulinumtoxinB), and Xeomin (incobotulinumtoxinA) is considered investigational for other indications, including but not limited to:
	• Neurological indications such as:
	  ○ Chronic motor tic disorder and tics associated with Tourette syndrome (motor tics)
	  ○ Essential tremor
	  ○ Headaches, except as noted above for Botox (onabotulinumtoxinA) for prevention of chronic migraine headache
	  ○ Tinnitus
	• Urological indications such as:
	  ○ Benign prostatic hyperplasia
	  ○ Chronic prostatic pain
	  ○ Detrusor sphincteric dyssynergia (after spinal cord injury)
	  ○ Interstitial cystitis
	• Pain due to multiple etiologies such as:
	  ○ Chronic low back pain

Drug	Investigational
	○ Joint pain ○ Lateral epicondylitis ○ Mechanical neck disorders ○ Myofascial pain syndrome ○ Neuropathic pain after neck dissection ○ Pain after hemorrhoidectomy or lumpectomy ○ Prevention of pain associated with breast reconstruction after mastectomy ○ Temporomandibular joint disorders ○ Trigeminal neuralgia • Ano-rectal conditions such as: ○ Anismus ○ Internal anal sphincter achalasia • Primary focal hyperhidrosis ○ Plantar ○ Craniofacial • Severe Secondary gustatory hyperhidrosis • Other miscellaneous conditions such as: ○ Acquired nystagmus ○ Brachial plexus palsy ○ Bruxism ○ Cricopharyngeal dysphagia ○ Depression ○ Esophageal spasm ○ Facial wound healing ○ Gastroparesis ○ Nasal hypersecretion ○ Pelvic floor spasticity ○ Piriformis syndrome ○ Proctalgia fugax ○ Thyroid associated ophthalmopathy

Approval	Criteria
Initial authorization	**All covered uses for Botox (onabotulinumtoxinA), Daxxify (daxibotulinumtoxinA-lanm), Dysport (abobotulinumtoxinA), Myobloc (rimabotulinumtoxinB), and Xeomin**

Approval	Criteria
	(incobotulinumtoxinA) listed in policy may be approved up to 1 year.
Re-authorization criteria	**Botox (onabotulinumtoxinA) for the prophylaxis of chronic migraine headaches will be approved for 3 years as long as the individual has shown and continues to show:** • Sustained reduction in frequency of headache days compared with pretreatment level **OR** • Sustained reduction in headache duration compared with pretreatment level **Future re-authorization of Botox (onabotulinumtoxinA) for all covered indications in policy, except prophylaxis of chronic migraine headaches, may be approved up to 3 years as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.** **Future re-authorization of Daxxify (daxibotulinumtoxinA-lanm), Dysport (abobotulinumtoxinA), Myobloc (rimabotulinumtoxinB), and Xeomin (incobotulinumtoxinA) for all covered indications in policy may be approved up to 3 years as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Coding guidelines for this policy: When HCPCS code J0585, J0586, J0587, or J0588 is denied, the related injection codes(s) will also be subject to denial.

CPT 64640 may be requested/billed for treatment of the medical conditions of laryngeal and/or oromandibular dystonia reviewed in this policy.

Coding

Code	Description
CPT	
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance (e.g., when used for the treatment of gastroparesis)
46505	Chemodenervation of internal anal sphincter
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder
64611	Chemodenervation of parotid and submandibular salivary glands, bilateral
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (e.g., for blepharospasm, hemifacial spasm)
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (e.g., for chronic migraine)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (e.g., for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous (e.g., for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64642	Chemodenervation of one extremity; 1-4 muscle(s)
64643	Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
64644	Chemodenervation of one extremity; 5 or more muscles
64645	Chemodenervation of one extremity; each additional extremity, 5 or more muscles (List separately in addition to code for primary procedure)
64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)
64647	Chemodenervation of trunk muscle(s); 6 or more muscles
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (e.g., scalp, face, neck), per day
67345	Chemodenervation of extraocular muscle
Code	**Description**
HCPCS	
C9160	Injection, daxibotulinumtoxina-lanm, (Daxxify) 1 unit (code termed 4/1/2024)
J0585	Injection, onabotulinumtoxinA, (Botox) 1 unit
J0586	Injection, abobotulinumtoxinA, (Dysport) 5 units
J0587	Injection, rimabotulinumtoxinB, (Myobloc) 100 units

Code	Description
J0588	Injection, incobotulinumtoxinA, (Xeomin) 1 unit
J0589	Injection, daxibotulinumtoxina-lanm (Daxxify), 1 unit (new code effective 4/1/2024)
J3590	Unclassified biologics (Use to report Letybo and Jeuveau)
S2340	Chemodenervation of abductor muscle(s) of vocal cord
S2341	Chemodenervation of adductor muscle(s) of vocal cord

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Electromyographic guidance may be used to direct the injection of the botulinum toxin, particularly for treatment of the larynx or esophagus. Since 2006, there has been a CPT code for needle electromyographic guidance for chemodenervation (code 95874), as well as a code for electrical stimulation guidance (code 95873). Consideration of the guidance codes should be based on whether the botulinum toxin is being used for a medically necessary indication.

Injection of the vocal cords is done in association with laryngoscopic guidance. As indicated by the CPT code (31513, 31570, or 31571), laryngoscopy is considered an integral part of the procedure, and separate billing for laryngoscopy and injection is not warranted.

Botulinum toxin as a treatment of achalasia requires a separate endoscopy procedure, which is billed separately.

Definition of Terms

For the purposes of this policy, the following definitions apply:

Cosmetic: Cosmetic services are those which are primarily intended to preserve or improve appearance. Cosmetic surgery is performed to reshape structures of the body in order to improve the individual's appearance or self-esteem.

Physical functional impairment: In this policy, functional impairment means a limitation from normal (or baseline level) of physical functioning that may include, but is not limited to,

problems with ambulation, mobilization, communication, respiration, eating, swallowing, vision, facial expression, skin integrity, distortion of nearby body parts or obstruction of an orifice. The physical functional impairment can be due to structure, congenital deformity, pain, or other causes. Physical functional impairment excludes social, emotional and psychological impairments or potential impairments.

Reconstructive surgery: In this policy, reconstructive surgery refers to surgeries performed on abnormal structures of the body, caused by congenital defects, developmental abnormalities, trauma, infection, tumors or disease. It is generally performed to improve function.

Primary focal hyperhidrosis: : A multispecialty working group defined primary focal hyperhidrosis as a condition characterized by visible, excessive sweating of at least 6 months in duration without apparent cause and with at least 2 of the following features:

- Age at onset younger than 25 years
- Bilateral and relatively symmetric sweating
- Cessation of focal sweating during sleep
- Frequency of at least once per week
- Impairment of daily activities
- Positive family history

Consideration of Age

Age limits specified in this policy are determined according to FDA-approved indications, where applicable.

Benefit Application

Botox (onabotulinumtoxinA), Daxxify (daxibotulinumtoxinA-lanm), Dysport (abobotulinumtoxinA), Myobloc (rimabotulinumtoxinB), and Xeomin (incobotulinumtoxinA) are managed under the medical benefit.

Description

Botulinum is a family of toxins produced by the anaerobic organism Clostridium botulinum. There are seven known serotypes of botulinum toxin: types A, B, C-1, D, E, F, and G. All botulinum toxins inhibit the release of acetylcholine from peripheral cholinergic nerve endings, there-by blocking neuromuscular and salivary neuroglandular cholinergic activity. Following injection, increased muscle tone typically returns within 3-4 months and glandular activity within 4-6 months.

Background

Four distinct serotype A botulinum toxin products, Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Jeuveau (prabotulinumtoxinA), Letybo (letibotulinumtoxinA-wlbg), and Xeomin (incobotulinumtoxinA) and one serotype B botulinum toxin product, Myobloc (rimabotulinumtoxinB), have been approved by the US Food and Drug Administration (FDA). Due to the unique manufacturing process used to produce each product, they are chemically, pharmacologically, and potentially clinically distinct. Moreover, units of biological activity are unique to each botulinum toxin product and cannot be compared or converted into units of another product, i.e., one unit of Botox is not equal to one unit of Dysport, one unit of Xeomin, or one unit of Myobloc. In addition, there are no universally accepted safe dose conversion ratios. Failure to recognize the unique characteristics of each formulation may lead to undesired individual outcomes.

Table 1. FDA Indications of the Botulinum Toxin Products

FDA Approved Indication	Botox	Dysport	Myobloc	Xeomin	Daxxify
Overactive bladder (adults)	X				
Urinary incontinence (adults)	X				
Neurogenic detrusor overactivity	X[a]				
Limb spasticity (adults)	X[b]	X[b]		X[c]	
Limb spasticity (pediatrics)	X[d]	X[d]		X[e]	
Chronic migraine (adults)	X				

FDA Approved Indication	Botox	Dysport	Myobloc	Xeomin	Daxxify
Cervical dystonia (adults)	X	X	X	X	X
Severe axillary hyperhidrosis (adults)	X				
Blepharospasm (adults)	X			X	
Blepharospasm (pediatrics)	X[f]				
Strabismus	X[f]				
Chronic Sialorrhea (adults)			X	X	
Chronic Sialorrhea (pediatrics)				X[g]	

FDA: US Food and Drug Administration.
a ≥ 5 years of age
b Upper and lower limb
c Upper limb
d Upper and lower limb ≥2 years of age.
e Upper limb 2 to 17 years of age. Excludes spasticity caused by cerebral palsy.
f ≥12 years of age
g ≥ 2 years of age

Antibody formation

Botulinum toxin products are proteins; as such, they carry an inherent risk for development of anti-drug antibodies, although few have been neutralizing (0%-6%) depending on the product, condition being treated, treatment duration, and dose.

Because botulinum toxin serotypes show approximately 40% homology on comparison of amino acid sequencing, crossreactive antibodies could develop. However, to date, all crossreactive antibodies described for botulinum toxins have been non-neutralizing. A panel of botulinum toxin researchers has published a consensus statement that indicates that cross-neutralization between anti-toxin A and anti-toxin B-G does not occur. Switching serotypes is a well-established management strategy in the face of resistance due to neutralizing antibodies. Clinical studies of individuals resistant to type A toxin have been shown to benefit from injection of type B, and at doses no higher than those required by toxin-naïve individuals.

Incobotulinumtoxin A (Xeomin) has a different manufacturing process that purportedly yields purified neurotoxin without accessory proteins, which may result in less immunogenicity. However, this remains to be established.

Summary of Evidence for Off-Label Use

Esophageal Achalasia

Esophageal achalasia results from progressive degeneration of ganglion cells in the myenteric plexus in the esophageal wall, leading to failure of relaxation of the lower esophageal sphincter, accompanied by a loss of peristalsis in the distal esophagus. Treatment is aimed at decreasing the resting pressure in the lower esophageal sphincter to a level at which the sphincter no longer impedes the passage of ingested material and this can be achieved by 2 ways: 1) mechanical disruption of the muscle fibers of the lower esophageal sphincter pneumatic dilation (PD), surgical myotomy or peroral endoscopic myotomy and 2) Pharmacological reduction in lower esophageal sphincter pressure (e.g., injection of botulinum toxin or use of oral nitrates).

A Cochrane review by Leyden et al (2014) identified 7 RCTs (total n=178 participants) that compared onabotulinumtoxinA with endoscopic PD. Outcomes reported was symptom remission rate at 1, 6 and 12 months. The meta-analysis of RCTs showed no difference in relative risk (RR) of symptom remission at 1 month between PD vs onabotulinumtoxinA. (RR=1.11, 95% confidence interval [CI]: 0.97 to 1.27). However, at 6 and 12 months, PD resulted in higher symptom remission rates and the difference was statistically significant (RR=1.57, p<0.005; RR=1.88, p= <0.005). No serious adverse events were reported after onabotulinumtoxinA injection; however, there were 3 cases of perforation after PD. Authors concluded that PD resulted in superior long-term efficacy compared with onabotulinumtoxinA (at 6 and 12 months). While the overall methodological quality of the individual RCTs was reported to be good, the risk of bias was high. In particular, only 1 RCT was double blind, 5 RCTs were potentially at a risk of selection, performance or detection bias due to inappropriate allocation of concealment, blinding of participants and personnel, and outcome assessment.

Wang et al (2009) conducted a meta-analysis of RCTs that compared the efficacy of different treatments for primary achalasia. Five RCTs compared botulinum toxin A injection with PD in individuals with untreated achalasia, and also examined both subjective and objective parameters of esophageal improvement in all individuals over 12 months. Authors reported that symptom remission rate was significantly higher in individuals treated with PD vs botulinum toxin A injection (65.8% vs 36% respectively. The proportion of individuals who relapsed within a year was 16.7% with PD vs 50% with botulinum toxin injection. Moreover, relapse time of botulinum toxin injection was shorter than that of PD after first therapy. Two RCTs compared efficacy of laparoscopic myotomy with botulinum toxin A injection in individuals with untreated achalasia. Authors reported that the symptom remission rate of botulinum toxin injection rapidly decreased and nearly 50% of individuals were symptomatic again after 1 year of treatment.

Laparoscopic myotomy had superior efficacy to botulinum toxin injection (laparoscopic myotomy 83.3% vs botulinum toxin injection 64.9%, RR 1.28; 95% CI 1.02-1.59; P=0.03). Individuals treated with onabotulinumtoxinA had more frequent relapse and shorter time to relapse than those treated with laparoscopic myotomy. Some limitations of this meta-analysis include small number of cohorts in each trial, poor randomization techniques, and inadequate follow-up.

While the evidence is suggestive that PD and surgical myotomy are definitive therapies for esophageal achalasia and associated with superior long-term outcomes compared with botulinum toxin A, in individuals who are not good candidates for PD and/or surgical myotomy, botulinum toxin A may be a reasonable option. Further, botulinum toxin injection has the advantage of being less invasive as compared with surgery, can be easily performed during routine endoscopy. Initial success rates with botulinum toxin are comparable to PD and surgical myotomy. However, individuals treated with botulinum toxin have more frequent relapses and a shorter time to relapse. Greater than 50% of individuals with achalasia treated with botulinum toxin A require retreatment within 6 to 12 months. Repeated botulinum toxin injections may also make a subsequent Heller myotomy more challenging.

Chronic Anal Fissure

An anal fissure is a tear or ulceration in the lining of the anal canal below the mucocutaneous junction. Chronic anal fissure is typically associated with anal spasm or high anal pressure. The initial treatment is medical management (combination of supportive measures such as high fiber diet, sitz bath, topical analgesic and 1 of the topical vasodilators such as nifedipine or nitroglycerin for 1 month). Individuals who fail medical therapy are candidates for surgical therapy that includes lateral internal sphincterotomy or botulinum toxin injection. Individuals who are at a high-risk for fecal incontinence such as women who have had multiple vaginal deliveries and older individuals with may have a weak anal sphincter complex are advised to undergo surgical procedures that do not require division of the anal sphincter muscle (e.g., botulinum toxin injection, fissurectomy, or anal advancement flap). Individuals who are not at risk for developing fecal incontinence may undergo lateral internal sphincterotomy, which is considered the most effective treatment for anal fissure.

Chen et al (2014) compared outcomes of onabotulinumtoxinA injection with lateral internal sphincterotomy based on 7 RCTs. Treatment with botulinum toxin injection was associated with a lower healing rate and a higher recurrence rate compared with lateral internal sphincterotomy. Sphincterotomy also resulted in higher complication rates but the difference was not statistically

significant (pvalue= 0.35). The meta-analysis suggests that internal sphincterotomy is more effective to treat anal fissure but onabotulinumtoxinA injection was associated with lower rates of incontinence. Authors reported multiple limitations in the evidence pooled for the meta-analysis including various dose of onabotulinumtoxinA used in different trials, inconsistent definition of chronic anal fissure used in the RCTs and none of the included RCTs were blinded. In addition, results of included studies were not consistent. The total complication rate varied from 0 to 64 % among the trials, while the incontinence rate varied from 0 to 48%. Nelson et al (2012) published a Cochrane review that compared multiple treatment options for chronic anal fissure. Reported results for comparison of botulinum toxin injection with sphincterotomy are consistent with those reported by Chen et al (2014). Botulinum toxin A injection is therefore preferably used for individuals who are at a high-risk of developing fecal incontinence (e.g., multiparous women or older individuals).

Hirschsprung Disease

Hirschsprung disease is a rare genetic birth defect that results in motor disorder of the gut due to failure of neural crest cells (precursors of enteric ganglion cells) to migrate completely during intestinal development during fetal life. The resulting aganglionic segment of the colon fails to relax, causing a functional obstruction.

A retrospective case series by Han-Geurts et al (2014), included 33 children with surgically treated Hirschsprung disease treated with intrasphincteric botulinum toxin A injections for obstructive symptoms was analyzed with a retrospective chart review between 2002 and 2013 in the Netherlands. The mean age at time of botulinum toxin A treatment was 3.6 years and median follow-up was 7.3 years (range 1 to 24). A median of 2 (range 1–5) injections were given. Initial short-term improvement was achieved in 76%, with a median duration of 4.1 months (range 1.7 to 58.8). The proportion of children hospitalized for enterocolitis decreased after treatment from 19 to 7. More than half (51%) of individuals reported good or excellent long-term outcomes after a median follow-up of 126 months. Two children experienced complications: transient pelvic muscle paresis with impairment of walking. In both children symptoms resolved within 4 months without treatment.

A prospective case series by Minkes and Langer (2000), included 18 children (median age, 4 years) with persistent obstructive symptoms after surgery for Hirschsprung disease.7, Individuals received injections of onabotulinumtoxinA into 4 quadrants of the sphincter. The total dose of onabotulinumtoxinA during the initial series of injections was 15 to 60 U. Twelve (67%) of 18 individuals improved for more than 1 month and the remaining 6 (33%) either showed no

improvement or improved for less than 1 month. Ten children had 1 to 5 additional injections due to either treatment failure or recurrence of symptoms; retreatment was not based on a standardized protocol.

A retrospective case series by Patruset al (2011) reviewed outcomes in 22 individuals with Hirschsprung disease treated over 10 years; subject had received a median of 2 (range, 1-23) onabotulinumtoxinA injections for postsurgical obstructive symptoms. Median follow-up (time from first injection to time of chart review) was 5 years (range, 0-10 years). At chart review, 2 (9%) of 22 individuals had persistent symptoms. Eighteen (80%) children had a "good response" to the initial treatment (not defined), and 15 (68%) had additional injections. The authors reported that the number of hospitalizations for obstructive symptoms decreased significantly after onabotulinumtoxinA injection (median, 0) compared with preinjection (median, 1.5; p=0.003). The authors did not report whether individuals received other treatments during the follow-up period in either case series.

Tension and Cervicogenic Headache

The meta-analysis by Jackson et al (2012) identified 8 RCTs evaluating onabotulinumtoxinA (6 trials) and abobotulinumtoxinA (2 trials) for treating chronic tension-type headaches; all were placebo-controlled. A pooled analysis of these 8 studies did not find a statistically significant difference in change in the monthly number of headache days in the botulinum toxin group vs the placebo group (difference=-1.43; 95% CI, -3.13 to 0.27; p-value=0.02).

Silberstein et al (2006)15, randomized 300 individuals to onabotulinumtoxinA (5 different doses) or placebo for the prophylaxis of chronic tension-type headache. The trial failed to demonstrate statistically significant difference between the onabotulinumtoxinA groups and the placebo group in the number of headache free days per month.

Multiple RCT's with smaller sample size (<50) have evaluated the efficacy of onabotulinumtoxinA in individuals with cervicogenic headache but either reported a lack of treatment benefit or were methodological flawed (pain scores imbalanced at baseline) to derive meaningful conclusions.

Essential Tremor

Botulinum toxin type A (BoNT-A) have been shown to provide benefit for limb tremor associated with essential tremor but have been associated with dose-dependent hand weakness. A

systematic review published in 2011, concluded that botulinum toxin A is possibly effective for the treatment of essential hand tremor, with a beneficial effect that was modest at best. The conclusion was drawn on the basis of 2 double-blind, placebo-controlled, parallel-design trials of botulinum toxin type A- one enrolled 25 individuals and the other enrolled 133 individuals. In the first trial, 11 of 12 treated individuals reported mild (50%) or moderate (42%) wrist or finger weakness. In the second trial, symptomatic hand weakness occurred in 30% of the low-dose group and 70% of the high-dose group. Neither the investigators nor the individuals reported any subjective benefit, and there was minimal (0·5 points) change at 6 weeks. Subsequent to this systematic review, Mittal et al (2017) published the results of a small, randomized trial of 30 individuals with essential tremor and Parkinson disease tremor to incobotulinumtoxinA in a crossover design. Statistically significant improvements in clinical rating scores of rest tremor and tremor severity at 4 and 8 weeks were reported in the treated individuals and of action/postural tremor at 8 weeks; however, there was no statistically significant difference in grip strength at 4 weeks between the 2 groups. The clinical significance of small benefits observed in trials that were offset by frequent adverse effects (hand weakness) do not permit conclusions about net heath benefit. A larger trial with longer term follow-up is required to replicate these findings and provide long-term follow-up to mitigate the risk of developing hand weakness over the course of time.

Tinnitus

Slengerik-Hansen et al (2016) reported the findings of a systematic review that included 22 studies, mainly case reports and case series with a total of 51 treated individuals treated with onabotulinumtoxinA for the treatment of tinnitus. A small (n=30) cross over prospective study by Stidham et al (2005) reported statistically significant decrease in tinnitus handicap inventory scores between pretreatment and 4 month post botulinum toxin A injection. Multiple other outcomes studies showed no difference. Well-conducted RCTs with sufficiently large sample sizes are needed.

Trigeminal Neuralgia

Evidence for the efficacy and safety of botulinum toxin A for trigeminal neuralgia is limited and was summarized by Morral et al (2016) in a systematic review that included 4 RCTs (total n=178 individuals). The largest trial randomly assigned 80 individuals to either botulinum toxin A or placebo. While the meta-analysis reported significant reductions in mean pain scores and attack

frequency in the botulinum toxin A compared with the placebo group, there are concerns about small individual numbers, limited durability and quality of evidence.

Benign Prostatic Hyperplasia

Marchal et al (2012) reported the results of a systematic review on use of onabotulinumtoxinA and abobotulinumtoxinA to treat benign prostatic hyperplasia. Two clinical trials with sufficient quality were selected for meta-analysis reported no difference in pre- and post-treatment of maximum flow, prostate volume, International Prostate Symptom Score and prostate-specific antigen post-voiding residue.

Interstitial Cystitis

The mechanism of the effect of Intradetrusor botulinum toxin therapy for interstitial cystitis is likely the ability of botulinum toxin to modulate sensory neurotransmission. While botulinum toxin has been shown to alleviate symptoms in multiple studies mostly conducted outside of the U. S., there is a risk of urinary retention which may be particularly devastating for an individual with a painful bladder and therefore any individual considering this treatment must be willing and able to perform intermittent self-catheterization.

A network meta-analysis of 16 trials including 905 individuals published in 2016 indicated that botulinum toxin-A treatment had the highest probability of being the best treatment course based on global response assessment and significantly ameliorates bladder capacity in individuals with interstitial cystitis.31, However, botulinum toxin A showed no treatment advantages with regard to pain, urinary frequency, and urgency results. Wang et al (2016) who reported the findings of a systematic review that included 7 RCTs and a retrospective study on onabotulinumtoxinA and abobotulinumtoxinA rated only 1 of the 7 RCTs as high-quality (i.e., low-risk of bias) while 5 were rated as moderate, and the other was rated as a high-risk of bias. Kuo et al (2016) reported the results of an RCT that included 60 Taiwanese individuals (52 women, 8 men) with IC/painful bladder syndrome who had failed at least 6 months of conventional therapy. In this trial, at a higher dose (200 units of botulinum toxin A), adverse reactions occurred in 9 of 15 individuals (4 individuals had acute or chronic urinary retention, 7 had severe dysuria). Later, the dose was decreased to 100 units that resulted in reduction of adverse events but they still occurred more frequent than hydrodistention alone.

Lateral Epicondylitis

Although the mechanism for action for botulinum toxin in epicondylitis is not clearly understood, it is thought to be as "proinflammatory". Botulinum toxin has been evaluated as a treatment for epicondylitis in a number of RCTs as summarized in a number of systematic reviews. In the systematic review and meta-analysis published by Lin et al (2019), authors included 6 RCTs (n=321) that comparing onabotulinumtoxinA or abobotulinumtoxinA with placebo or corticosteroid injections in individuals with lateral epicondylitis. Four of the 6 trials enrolled less than 30 participants per treatment arm and allocation concealment was unclear in 4 out of 6 trials. Results were reported as standardized mean differences and a negative number implied a favorable effect of botulinum toxin on pain reduction.

Compared with placebo, botulinum toxin injection significantly reduced pain at all 3 time points (2 to 4 weeks, 8 to 12 weeks and at 16 weeks or more; standardized mean difference -0.73 (-1.29 to -0.17), -0.45 (-0.74 to -0.15) and -0.54 (-0.99 to -0.11) respectively. In contrast, botulinum toxin was significantly less effective than corticosteroid 2 to 4 weeks following injection; standardized mean difference 1.15 (0.57 to 1.34) with no difference at 8-12 weeks or 16 weeks or more time point. While the systematic reviews generally report pain relief in individual trials of botulinum toxin vs the comparator, treatment with botulinum toxin was associated with temporary paresis of finger extension.

Myofascial Pain Syndrome

Several systematic reviews of RCTs have evaluated onabotulinumtoxinA and abobotulinumtoxinA for myofascial pain syndrome. The Cochrane systematic review by Soares et al (2014) identified 4 placebo-controlled, double-blind RCTs that included 233 participants with myofascial pain syndrome excluding neck and head muscles. Due to heterogeneity among studies, reviewers did not pool analyses. The primary outcomes were change in pain as assessed by validated instruments. Three of the 4 studies found that botulinum toxin did not significantly reduce pain intensity. Major limitations included high-risk of bias due to study size in 3 of the 4 studies and selective reporting in 1 study. Two other systematic reviews that focused on myofascial pain syndrome involving head and neck muscles reported similar findings. Systematic review by Desai et al (2014) included 7 trials that evaluated the efficacy of botulinum toxin type A in cervico-thoracic myofascial pain syndrome. The majority of studies found negative results and except for 1, 6 identified trials had significant failings due to deficiencies in 1 or more major quality criteria.

Low Back Pain

Foster et al (2001) reported the findings of an RCT in which 31 consecutive individuals with chronic low back pain of at least 6 months in duration were randomized to onabotulinumtoxinA or saline. Botulinum toxin A was superior to placebo injection for pain relief and improved function at 3 and 8 weeks (50 % pain relief at 3 weeks 73.3 vs 25%; at 8 weeks 60 vs 16%, respectively). However, in most individuals, benefits were no longer present after 3 to 4 months. These results should be considered preliminary, and further data from randomized trials are needed to confirm findings in a larger number of individuals over a longer duration and to evaluate benefits and harms of repeated injections before this treatment can be recommended.

Temporomandibular Joint Disorders

Chen et al (2015) summarized the evidence assessing the efficacy of botulinum toxin A for treatment of temporomandibular joint disorders in a systematic review that included 5 RCTs. Sample size in majority of trials was 30 or less except for 1. Three of the 5 studies were judged to be at high-risk of bias. All studies administered a single injection of onabotulinumtoxinA or abobotulinumtoxinA and followed individuals up at least 1 month later. Four studies used a placebo (normal saline) control group and the fifth used abobotulinumtoxinA to fascial manipulation. Data were not pooled due to heterogeneity among trials. In a qualitative review of the studies, 2 of the 5 trials found a significant short-term (1-2 months) benefit of onabotulinumtoxinA compared with control on pain reduction.

Post Hemorrhoidectomy Pain

Several small RCTs of botulinum toxin intrasphincter injection for controlling pain after hemorrhoidectomy have been published. A trial by Patti et al (2005) randomized 30 individuals to onabotulinumtoxinA 20 U or saline injection and reported a significantly shorter duration of postoperative pain at rest and during defecation in the treated group. A trial by Patti et al (2006), which also included 30 individuals, found significant differences in postoperative maximum resting pressure change from baseline with onabotulinumtoxinA vs topical glyceryl trinitrate ($p<0.001$). In addition, there was a significant reduction in postoperative pain at rest ($p=0.01$) but not during defecation. There was no difference in healing.

Pelvic and Genital Pain in Women

One double-blind, randomized, placebo-controlled trial by Abbott et al (2006) evaluated 60 women with chronic pelvic pain and pelvic floor spasm. Individuals received injections of onabotulinumtoxinA or placebo. Pain scores were reduced for both groups, but there were no significant differences between groups. The trial likely was underpowered to detect clinically significant differences in outcomes between groups.

Internal Anal Sphincter Achalasia

Friedmacher and Puri (2012) reported results of a meta-analysis that included 395 individuals from 2 prospective and 14 retrospective case series that compared internal anal sphincter myectomy (n=229) with botulinum A injection (n=166). Regular bowel movements (odds ratio [OR]=0.53; 95% CI 0.29 to 0.99, p = 0.04), short-improvements (OR=0.56; 95% CI 0.32 to 0.97, p = 0.04) and long-term improvement (OR=0.25; 95% CI 0.15 to 0.41, p < 0.0001) favored myectomy compared with botulinum toxin A injection. Further, rate of transient fecal incontinence (OR=0.07, 95% CI 0.01 to 0.54; p < 0.01), rate of non-response (OR 0.52, [95 % CI 0.27-0.99]; p=0.04) and subsequent surgical treatment (OR 0.18, [95 % CI 0.07-0.44]; p < 0.0001) was significantly higher with botulinum A injection compared with myectomy. There was no significant difference in continued use of laxatives or rectal enemas, overall complication rates, constipation and soiling between the 2 procedures. Authors concluded that myectomy was a more effective treatment option compared with intrasphincteric botulinum toxin A injection.

Anismus

Emile et al (2016) reported on the results of a systematic review that assessed 7 studies comprising 189 individuals with a follow-up period greater than 6 months in each study. Of the 7 studies, 2 were RCTs and the others comparative and observational studies. Both RCTs were single-site from the same author group and conducted in Egypt, enrolling 15 and 24 individuals, respectively. Improvement was defined as individuals returning to their normal habits. The first RCT used biofeedback and the other used surgery as the comparator. In the first RCT, 50% of individuals in the biofeedback group reported improvement initially at 1 month but it dropped down to 25% by the end of year. The respective proportions of individuals in the botulinum toxin arm were 70.8% and 33.3%. In the second RCT, surgery improved outcomes in all

individuals at 1 month but that percentage dropped to 66.6% at 1 year. The respective proportions of individuals in the botulinum toxin arm were 87% and 40%, respectively. While these results would suggest temporary improvement, methodologic limitations, including small sample size and lack of blinded assessment, limit the interpretation of these RCTs.

Gastroparesis

A systematic review by Bai et al (2010) identified 15 studies on onabotulinumtoxinA to treat gastroparesis. Two studies were RCTs; the remainder was case series or open-label observational studies. Reviewers stated that, while the nonrandomized studies generally found improvements in subjective symptoms and gastric emptying after onabotulinumtoxinA injections, the RCTs did not report treatment benefit with onabotulinumtoxinA for treating gastroparesis. The 2 RCTs were inadequately powered RCTs; one included 23 individuals and the other included 32 individuals. Additional adequately powered RCTs are needed.

Depression

Magid et al (2015) published a pooled analysis50, of individual patient data from 3 randomized trials evaluating injections of onabotulinumtoxinA in the glabellar region (forehead) for treating unipolar major depressive disorder as an adjunctive treatment. The response rate (defined as ≥ 50% improvement from baseline scores in the depression score) was higher in the onabotulinumtoxinA group compared with placebo (54.2% vs 10.7%; OR=11.1; 95% CI 4.3 to 28.8). The respective remission rate (defined as score ≤ 7 for the Hamilton Depression Rating scales, ≤ 10 for the Montgomery-Asberg Depression Rating Scale) was 30.5% vs 6.7% (7.3; 95% CI, 2.4 to 22.5). While the effect size of the treatment observed in the pooled analysis and individual RCTs is clinically meaningful and large, there are multiple limitations that preclude drawing meaningful conclusions about net health benefit. Limitations in study design and conduct include potential of unblinding due to changes in cosmetic appearance, small sample size, lack of power analysis, short duration of follow-up in 2 out of 3 RCTs,52,51, lack of clarity on allocation concealment and lack of intention-to-treat analysis. More importantly, individuals with a history of major depressive order presenting with acute depression episode prior to enrollment in the trial were evaluated, it is unclear if botulinum toxin A treatment is intended to be used as a short-term treatment of a depressive episode or as a maintenance treatment for depression. Further, a large trial (NCT02116361) with 258 individuals to evaluate the efficacy of onabotulinumtoxinA as treatment for major depressive disorder in adult females was completed in 2016 but has not been published which raises concerns about potential for publication bias.

Facial Wound Healing

Ziade et al (2013) reported results of an RCT in which 30 adults presenting to the emergency department with facial wounds without tissue loss were assigned to single an injection of onabotulinumtoxinA (n=11) or no injection (n=13) within 72 hours of the suturing of the wounds. Scars were assessed at a 1 year follow-up visit by individuals, an independent evaluator as well as a board of 6 experienced medical specialists. There were no significant differences between the 2 groups in multiple outcomes that were assessed. The limitations of the study included relatively small sample size, lost to follow-up of 20% individuals and lack of individuals blinding. Gassner et al (2006) reported the results of another RCT that randomized 31 individuals to onabotulinumtoxinA- or placebo-induced immobilization of facial lacerations to improve wound healing. Blinded assessment of standardized photographs by experienced facial plastic surgeons using a 10-cm visual analog scale at 6 months served as the main outcome measure. The difference in visual scores was 8.9 in the treatment arm vs 7.2 in the placebo arm (p=0.003). Limitations of the study included a single-institution study, relatively small sample size, lack of clarity on number screened/randomized/excluded from the final analysis.

Practice Guidelines and Position Statements

American Urological Association

In 2019, the American Urological Association guideline on non-neurogenic overactive bladder states, "clinicians may offer intradetrusor onabotulinumtoxinA (100U) as third-line treatment in the carefully-selected and thoroughly-counseled individual who has been refractory to first- and second-line overactive bladder treatments. The individual must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization if necessary. Standard (Evidence Strength Grade B)."

In 2014, the American Urological Association guideline on diagnosis and treatment of interstitial cystitis/bladder pain syndrome states, "intradetrusor botulinum toxin A may be administered if other treatments have not provided adequate symptom control and quality of life or if the clinician and individual agree that symptoms require this approach. Individuals must be willing to accept the possibility that post-treatment intermittent self- catheterization may be necessary. Option (Evidence Strength C)".

American Academy of Neurology

In 2016, the American Academy of Neurology updated its practice guidelines on use of botulinum toxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and chronic headache. Recommendations are summarized in **Table 2**.

Table 2. Recommendations for Use of Botulinum Toxin to Treat Various Disorders

Recommendation	LOR
Blepharospasm	
OnabotulinumtoxinA and incobotulinumtoxinA injections should be considered	B
AbobotulinumtoxinA may be considered	C
Cervical dystonia	
AbobotulinumtoxinA and rimabotulinumtoxinB should be offered	A
OnabotulinumtoxinA and incobotulinumtoxinA should be considered	B
Focal manifestations of adult spasticity involving the upper limb	
AbobotulinumtoxinA, incobotulinumtoxin A, and onabotulinumtoxinA should be offered	A
RimabotulinumtoxinB should be considered as treatment options.	B
OnabotulinumtoxinA should be considered as a treatment option before tizanidine for treating adult upper-extremity spasticity	B
For focal manifestations of adult spasticity involving the lower limb	
OnabotulinumtoxinA and abobotulinumtoxinA should be offered as treatment options.	A
There is insufficient evidence to support or refute a benefit of incobotulinumtoxinA or rimabotulinumtoxinB for treatment of adult lower-limb spasticity	
Headache	
To increase the number of headache-free days, onabotulinumtoxinA should be offered as a treatment option to individuals with chronic headaches.	A
OnabotulinumtoxinA should be considered to reduce headache impact on health-related quality of life. Chronic migraine refers to migraine attacks occurring 15 days or more monthly for at least 3 months, with attacks lasting 4 hours or more.	B
OnabotulinumtoxinA should not be offered as a treatment for episodic migraines. Episodic migraine refers to migraine with a lesser frequency of attack.	A

LOR: level of recommendation.

American Society of Colon and Rectal Surgeon

The revision of a practice parameter on the treatment of anal fissures by the American Society of Colon and Rectal Surgeons (2017) states, "Botulinum toxin has similar results compared with topical therapies as first-line therapy for chronic anal fissures, and modest improvement in healing rates as second-line therapy following treatment with topical therapies. Grade of Recommendation: Strong recommendation based on low- and very-low-quality evidence."

American Pediatric Surgical Association

In 2017, the American Pediatric Surgical Association published guidelines based on group discussions, literature review and expert consensus for the management of postoperative obstructive symptoms in children with Hirschsprung disease. These guidelines recommend that if there is no mechanical obstruction and rectal biopsy is normal, botulinum toxin injection into the internal anal sphincter should be tried. If an individual shows significant improvement, the individual can receive botulinum toxin injection every 3–6 months as many times as necessary depending on symptoms. In most cases, the symptoms will gradually improve with age.

References

1. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Cochrane Database Syst Rev. 2014; (12): CD005046. PMID 25485740
2. Wang L, Li YM, Li L. Meta-analysis of randomized and controlled treatment trials for achalasia. Dig Dis Sci. Nov 2009; 54(11): 2303-11. PMID 19107596
3. Smith CD, Stival A, Howell DL, et al. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. Ann Surg. May 2006; 243(5): 579-84; discussion 584-6. PMID 16632991
4. Chen HL, Woo XB, Wang HS, et al. Botulinum toxin injection versus lateral internal sphincterotomy for chronic anal fissure: a meta-analysis of randomized control trials. Tech Coloproctol. Aug 2014; 18(8): 693-8. PMID 24500725
5. Nelson RL, Thomas K, Morgan J, et al. Non surgical therapy for anal fissure. Cochrane Database Syst Rev. Feb 15 2012; (2): CD003431. PMID 22336789
6. Koivusalo AI, Pakarinen MP, Rintala RJ. Botox injection treatment for anal outlet obstruction in patients with internal anal sphincter achalasia and Hirschsprung's disease. Pediatr Surg Int. Oct 2009; 25(10): 873-6. PMID 19662428
7. Minkes RK, Langer JC. A prospective study of botulinum toxin for internal anal sphincter hypertonicity in children with Hirschsprung's disease. J Pediatr Surg. Dec 2000; 35(12): 1733-6. PMID 11101725
8. Patrus B, Nasr A, Langer JC, et al. Intrasphincteric botulinum toxin decreases the rate of hospitalization for postoperative obstructive symptoms in children with Hirschsprung disease. J Pediatr Surg. Jan 2011; 46(1): 184-7. PMID 21238663

9. Han-Geurts IJ, Hendrix VC, de Blaauw I, et al. Outcome after anal intrasphincteric Botox injection in children with surgically treated Hirschsprung disease. J Pediatr Gastroenterol Nutr. Nov 2014; 59(5): 604-7. PMID 25000353

10. Bendtsen L, Evers S, Linde M, et al. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. Eur J Neurol. Nov 2010; 17(11): 1318-25. PMID 20482606

11. Wieckiewicz M, Grychowska N, Zietek M, et al. Evidence to Use Botulinum Toxin Injections in Tension-Type Headache Management: A Systematic Review. Toxins (Basel). Nov 15 2017; 9(11). PMID 29140286

12. Bogduk N, Govind J. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. Lancet Neurol. Oct 2009; 8(10): 959-68. PMID 19747657

13. Hanno PM, Erickson D, Moldwin R, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment. J Urol. May 2015; 193(5): 1545-53. PMID 25623737

14. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. Apr 25 2012; 307(16): 1736-45. PMID 22535858

15. Silberstein SD, Gobel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tensiontype headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia. Jul 2006; 26(7): 790-800. PMID 16776693

16. Linde M, Hagen K, Salvesen O, et al. Onabotulinum toxin A treatment of cervicogenic headache: a randomised, double-blind, placebo-controlled crossover study. Cephalalgia. May 2011; 31(7): 797-807. PMID 21300635

17. Braker C, Yariv S, Adler R, et al. The analgesic effect of botulinum-toxin A on postwhiplash neck pain. Clin J Pain. Jan 2008; 24(1): 5-10. PMID 18180629

18. Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. Headache. Mar 2000; 40(3): 231-6. PMID 10759926

19. Padberg M, de Bruijn SF, Tavy DL. Neck pain in chronic whiplash syndrome treated with botulinum toxin. A doubleblind, placebo-controlled clinical trial. J Neurol. Mar 2007; 254(3): 290-5. PMID 17345052

20. Deuschl G, Raethjen J, Hellriegel H, et al. Treatment of patients with essential tremor. Lancet Neurol. Feb 2011; 10(2): 148-61. PMID 21256454

21. Jankovic J, Schwartz K, Clemence W, et al. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord. May 1996; 11(3): 250-6. PMID 8723140

22. Brin MF, Lyons KE, Doucette J, et al. A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. Neurology. Jun 12 2001; 56(11): 1523-8. PMID 11402109

23. Mittal SO, Machado D, Richardson D, et al. Botulinum Toxin in Parkinson Disease Tremor: A Randomized, Double-Blind, Placebo-Controlled Study With a Customized Injection Approach. Mayo Clin Proc. Sep 2017; 92(9): 1359-1367. PMID 28789780

24. Slengerik-Hansen J, Ovesen T. Botulinum Toxin Treatment of Objective Tinnitus Because of Essential Palatal Tremor: A Systematic Review. Otol Neurotol. Aug 2016; 37(7): 820-8. PMID 27273401

25. Stidham KR, Solomon PH, Roberson JB. Evaluation of botulinum toxin A in treatment of tinnitus. Otolaryngol Head Neck Surg. Jun 2005; 132(6): 883-9. PMID 15944559

26. Morra ME, Elgebaly A, Elmaraezy A, et al. Therapeutic efficacy and safety of Botulinum Toxin A Therapy in Trigeminal Neuralgia: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. Dec 2016; 17(1): 63. PMID 27377706

27. Marchal C, Perez JE, Herrera B, et al. The use of botulinum toxin in benign prostatic hyperplasia. Neurourol Urodyn. Jan 2012; 31(1): 86-92. PMID 21905088

28. Akiyama Y, Nomiya A, Niimi A, et al. Botulinum toxin type A injection for refractory interstitial cystitis: A randomized comparative study and predictors of treatment response. Int J Urol. Sep 2015; 22(9): 835-41. PMID 26041274

29. Kuo HC, Jiang YH, Tsai YC, et al. Intravesical botulinum toxin-A injections reduce bladder pain of interstitial cystitis/bladder pain syndrome refractory to conventional treatment - A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial. Neurourol Urodyn. Jun 2016; 35(5): 609-14. PMID 25914337

30. Manning J, Dwyer P, Rosamilia A, et al. A multicentre, prospective, randomised, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. Int Urogynecol J. May 2014; 25(5): 593-9. PMID 24276074

31. Zhang W, Deng X, Liu C, et al. Intravesical treatment for interstitial cystitis/painful bladder syndrome: a network meta-analysis. Int Urogynecol J. Apr 2017; 28(4): 515-525. PMID 27614759

32. Wang J, Wang Q, Wu Q, et al. Intravesical Botulinum Toxin A Injections for Bladder Pain Syndrome/Interstitial Cystitis: A Systematic Review and Meta-Analysis of Controlled Studies. Med Sci Monit. Sep 14 2016; 22: 3257-67. PMID 27624897

33. Lin YC, Wu WT, Hsu YC, et al. Comparative effectiveness of botulinum toxin versus non-surgical treatments for treating lateral epicondylitis: a systematic review and meta-analysis. Clin Rehabil. Feb 2018; 32(2): 131-145. PMID 28349703

34. Krogh TP, Bartels EM, Ellingsen T, et al. Comparative effectiveness of injection therapies in lateral epicondylitis: a systematic review and network meta-analysis of randomized controlled trials. Am J Sports Med. Jun 2013; 41(6): 1435-46. PMID 22972856

35. Sims SE, Miller K, Elfar JC, et al. Non-surgical treatment of lateral epicondylitis: a systematic review of randomized controlled trials. Hand (N Y). Dec 2014; 9(4): 419-46. PMID 25414603

36. Soares A, Andriolo RB, Atallah AN, et al. Botulinum toxin for myofascial pain syndromes in adults. Cochrane Database Syst Rev. Jul 25 2014; (7): CD007533. PMID 25062018

37. Desai MJ, Shkolnikova T, Nava A, et al. A critical appraisal of the evidence for botulinum toxin type A in the treatment for cervico-thoracic myofascial pain syndrome. Pain Pract. Feb 2014; 14(2): 185-95. PMID 23692187

38. Foster L, Clapp L, Erickson M, et al. Botulinum toxin A and chronic low back pain: a randomized, double-blind study. Neurology. May 22 2001; 56(10): 1290-3. PMID 11376175

39. Chen YW, Chiu YW, Chen CY, et al. Botulinum toxin therapy for temporomandibular joint disorders: a systematic review of randomized controlled trials. Int J Oral Maxillofac Surg. Aug 2015; 44(8): 1018-26. PMID 25920597

40. Patti R, Almasio PL, Muggeo VM, et al. Improvement of wound healing after hemorrhoidectomy: a double-blind, randomized study of botulinum toxin injection. Dis Colon Rectum. Dec 2005; 48(12): 2173-9. PMID 16400513

41. Patti R, Almasio PL, Luigi AP, et al. Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: a randomized trial. Dis Colon Rectum. Nov 2006; 49(11): 1741-8. PMID 16990976

42. Abbott JA, Jarvis SK, Lyons SD, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women: a randomized controlled trial. Obstet Gynecol. Oct 2006; 108(4): 915-23. PMID 17012454

43. Friedmacher F, Puri P. Comparison of posterior internal anal sphincter myectomy and intrasphincteric botulinum toxin injection for treatment of internal anal sphincter achalasia: a meta-analysis. Pediatr Surg Int. Aug 2012; 28(8): 765-71. PMID 22806601

44. Emile SH, Elfeki HA, Elbanna HG, et al. Efficacy and safety of botulinum toxin in treatment of anismus: A systematic review. World J Gastrointest Pharmacol Ther. Aug 06 2016; 7(3): 453-62. PMID 27602248

45. Farid M, El Monem HA, Omar W, et al. Comparative study between biofeedback retraining and botulinum neurotoxin in the treatment of anismus patients. Int J Colorectal Dis. Jan 2009; 24(1): 115-20. PMID 18719924

46. Farid M, Youssef T, Mahdy T, et al. Comparative study between botulinum toxin injection and partial division of puborectalis for treating anismus. Int J Colorectal Dis. Mar 2009; 24(3): 327-34. PMID 19039596

47. Bai Y, Xu MJ, Yang X, et al. A systematic review on intrapyloric botulinum toxin injection for gastroparesis. Digestion. 2010; 81(1): 27-34. PMID 20029206

48. Arts J, Holvoet L, Caenepeel P, et al. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. Aliment Pharmacol Ther. Nov 01 2007; 26(9): 1251-8. PMID 17944739

49. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum toxin A for the treatment of delayed gastric emptying. Am J Gastroenterol. Feb 2008; 103(2): 416-23. PMID 18070232

50. Magid M, Finzi E, Kruger TH, et al. Treating depression with botulinum toxin: a pooled analysis of randomized controlled trials. Pharmacopsychiatry. Sep 2015; 48(6): 205-10. PMID 26252721

51. Wollmer MA, de Boer C, Kalak N, et al. Facing depression with botulinum toxin: a randomized controlled trial. J Psychiatr Res. May 2012; 46(5): 574-81. PMID 22364892

52. Finzi E, Rosenthal NE. Treatment of depression with onabotulinumtoxinA: a randomized, double-blind, placebo controlled trial. J Psychiatr Res. May 2014; 52: 1-6. PMID 24345483

53. Magid M, Reichenberg JS, Poth PE, et al. Treatment of major depressive disorder using botulinum toxin A: a 24-week randomized, double-blind, placebo-controlled study. J Clin Psychiatry. Aug 2014; 75(8): 837-44. PMID 24910934

54. Ziade M, Domergue S, Batifol D, et al. Use of botulinum toxin type A to improve treatment of facial wounds: a prospective randomised study. J Plast Reconstr Aesthet Surg. Feb 2013; 66(2): 209-14. PMID 23102873

55. Gassner HG, Brissett AE, Otley CC, et al. Botulinum toxin to improve facial wound healing: A prospective, blinded, placebo-controlled study. Mayo Clin Proc. Aug 2006; 81(8): 1023-8. PMID 16901024

56. Lightner DJ, Gomelsky A, Souter L, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J Urol. Sep 2019; 202(3): 558-563. PMID 31039103

57. 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. May 10 2016; 86(19): 1818-26. PMID 27164716

58. Zesiewicz TA, Elble RJ, Louis ED, et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology. Nov 08 2011; 77(19): 1752-5. PMID 22013182

59. Stewart DB, Gaertner W, Glasgow S, et al. Clinical Practice Guideline for the Management of Anal Fissures. Dis Colon Rectum. Jan 2017; 60(1): 7-14. PMID 27926552

60. Langer JC, Rollins MD, Levitt M, et al. Guidelines for the management of postoperative obstructive symptoms in children with Hirschsprung disease. Pediatr Surg Int. May 2017; 33(5): 523-526. PMID 28180937

61. Arnon SS, Schecter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. JAMA. 2001;285:1059-1070.

62. Brin MF, Lew MR, Adler CH, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology. 1999;53(7):1431-1438.

63. Botox (onabotulinumtoxinA) Prescribing Information. Allergan USA, Inc.; Madison, NJ. Revised November 2023.

64. Dysport (abobotulinumtoxinA) Prescribing Information. Ipsen Biopharmaceuticals, Inc.; Cambridge, MA. Revised September 2023.

65. Jeuveau (prabotulinumtoxinA-xvfs) Prescribing Information. Evolus, Inc.; Newport Beach, CA. Revised April 2023.

66. Myobloc (rimabotulinumtoxinB) Prescribing Information. Solstice Neurosciences, LLC; Rockville, MD. Revised March 2021.

67. Xeomin (incobotulinumtoxinA) Prescribing Information. Merz Pharmaceuticals, LLC; Raleigh, NC. Revised September 2023.

68. Centers for Medicare & Medicaid Services. Local Coverage Article. Billing and Coding: Botulinum Toxin Types A and B policy. Article ID: A57185. Baltimore, MD. CMS. Effective 10/1/2019. Revised 1/1/2023. Available at URL: **https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=57185** . Accessed April 4, 2024.

69. Centers for Medicare & Medicaid Services. Local Coverage Article. Billing and Coding: Botulinum Toxin Article ID: A52848. Baltimore, MD. CMS. Effective 10/1/2015. Revised 1/5/2023. Available at URL: **https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=52848&ver=24&bc=CAAAAAAAAAAA**. Accessed April 4, 2024.

70. Daxxify (daxibotulinumtoxinA-lanm) Prescribing Information. Revance Therapeutics, Inc.; Nashville, TN. Revised August 2023.

71. Letybo (letibotulinumtoxinA-wlbg) Prescribing Information. Hugel; 61-20 Sinbuk-ro, Sinbuk-eup_Chuncheon, 24206 Korea.. Revised February 2024.

Appendix

Prophylactic Therapy

Antidepressants, Beta blockers, Calcium channel blockers, CGRP inhibitors (when used for migraine prophylaxis), Candesartan, Divalproex sodium, Gabapentin, Naproxen (when used daily), Topiramate, Valproic acid

History

Date	Comments
09/01/22	New policy, approved August 9, 2022, effective for dates of service on or after December 1, 2022, following 90-day provider notification. Added coverage for Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Myobloc (rimabotulinumtoxinB), and Xeomin (incobotulinumtoxinA).
03/01/23	Interim Review, approved February 14, 2023. Coding guideline notes added. References added. Added CPT codes: 46505, 52287, 64611, 64612, 64615, 64616, 64617, 64642, 64643, 64644, 64645, 64646, 64647, 67345 and HCPCS codes S2340, S2341. Changed the wording from "patient" to "individual" throughout the policy for standardization.
05/01/23	Annual Review, approved April 11, 2023. Added Daxxify (daxibotulinumtoxinA-lanm) use as cosmetic and not covered. Added Daxxify to HCPC code J3590. Added coverage for adults with hemifacial spasms to Myobloc, Xeomin, Dysport, and Botox. Clarified that headaches, except as noted in the policy for Botox for prevention of chronic migraine headache is considered investigational.
11/01/23	Interim Review, approved October 10, 2023. Added coverage for Daxxify (daxibotulinumtoxinA-lanm) for the treatment of cervical dystonia in adult individuals. Added coverage for Botox (onabotulinumtoxinA) for the treatment of adults with primary focal axillary or palmar hyperhidrosis (moved policy criteria from Policy 8.01.519 Nonpharmacologic Treatment of Hyperhidrosis to Policy 5.01.512). Updated policy criteria for Botox, Dysport, Myobloc, and Xeomin for the treatment of cervical dystonia requiring individual does not have acute cervical dystonia caused by exposure

Date	Comments
	to dopamine receptor-blocking drugs. Updated policy criteria for Botox, Dysport, Myobloc, and Xeomin become effective February 2, 2024 following 90-day provider notification. Added CPT codes 64650 and 64653. Updated Related Policy 8.01.519 – title changed from "Treatment of Hyperhidrosis" to "Nonpharmacologic Treatment of Hyperhidrosis".
11/07/23	Policy implementation delayed; the effective date of the policy is moved to February 7, 2024.
01/01/24	Coding update. Added new HCPCS code C9160.
02/01/24	Coding update. Added CPT code 43236.
04/01/24	Coding update. Termed HCPCS code C9160. Added new HCPCS code J0589.
05/01/24	Annual Review, approved April 22, 2024. Added Letybo (letibotulinumtoxinA-wlbg) use as cosmetic and not covered.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2024 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

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