



**BlueCross BlueShield
of Alabama**

Botulinum Toxin Medical Policy Prior Authorization

Precertification/Prior Authorization may be required under certain plans. Please verify each member's benefits.

OBJECTIVE

The intent of the botulinum toxin medical drug criteria is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling or supported in literature. The criteria will consider botulinum toxin appropriate for patients with a FDA labeled indication or indications supported in clinical studies and/or clinical guidelines. Dosing will be limited to the FDA labeled dosage for the specific indication or based on supported literature. Cosmetic uses for these agents are considered a benefit exclusion and will not be addressed in this criteria.

Target Drugs

Botox (onabotulinum toxin A)

Dysport (abobotulinum toxin A)

Myobloc (rimabotulinum toxin B)

Xeomin (incobotulinum toxin A)

Botox (onabotulinum toxin A) will be approved when following are met:

Initial Evaluation

1. The patient does not have any FDA labeled contraindications to the requested agent

AND

2. The patient has ONE of the following diagnoses:

a. Blepharospasm associated with dystonia (including benign essential blepharospasm or VII nerve disorders) AND the patient is >12 years of age

OR

b. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury) and BOTH of the following:

i. The patient's cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck

AND

ii. The patient has a history of recurrent involuntary contraction(s) of one or more of the muscles of the neck (e.g. sternocleidomastoid, splenius, trapezius, or posterior cervical muscles)

OR

c. Hemifacial spasm AND ONE of the following:

i. The patient has tried and failed one conventional prerequisite agent (e.g. carbamazepine, baclofen, and benzodiazepines)

OR

ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one conventional prerequisite agent

OR

d. Axillary hyperhidrosis AND ONE of the following:

i. The patient has tried and failed 20% aluminum chloride hexahydrate in absolute anhydrous ethyl alcohol (Drysol)

OR

- ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the prerequisite agent
- OR**
- e. Chronic migraine **AND** ALL of the following:
 - i. The patient has a diagnosis of chronic migraine as defined by BOTH of the following:
 - 1. ≥ 15 headache days per month of migraine-like or tension-like headache for a minimum of 3 months

AND

 - 2. ≥ 8 migraine headache days per month for a minimum of 3 months
 - ii. ONE of the following:
 - 1. The patient has failed at least TWO migraine prophylaxis classes (anticonvulsants [divalproex, valproate, topiramate], beta blockers [atenolol, metoprolol, nadolol, propranolol, timolol], antidepressants [amitriptyline, venlafaxine]) after an adequate trial as defined by BOTH of the following:
 - a. The trial length was at least 6 weeks at generally accepted doses

AND

 - b. The patient was $\geq 80\%$ adherent to the prophylaxis agent during the trial
 - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to an anticonvulsant, a beta blocker, AND an antidepressant listed above
 - iii. ONE of the following:
 - 1. The patient is not currently taking a calcitonin gene related peptide (CGRP) agent

OR

 - 2. The CGRP agent will be discontinued before starting the requested agent
 - iv. The patient will not be initiating a CGRP agent after starting therapy with the requested agent
 - v. The prescriber is a headache specialist (e.g. neurologist, The United Council for Neurologic Subspecialties [UCNS] certified) or has consulted with a headache specialist
 - vi. The patient has been evaluated for and does NOT have medication overuse headache
- OR**
- f. Neurogenic bladder with detrusor muscle overactivity **AND** ONE of the following:
 - i. The patient has tried and failed TWO first line conventional agent prerequisites: Needs to have tried one anticholinergic agent (e.g. oxybutynin, tolterodine, trospium, darifenacin, solifenacin or fesoterodine) **AND** Myrbetriq/mirabegron

OR

 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH an anticholinergic agent **AND** Myrbetriq/mirabegron
- OR**
- g. Strabismus (includes persistent cranial VI nerve palsy of one month or longer) **AND** ALL of the following:
 - i. The patient has had an inadequate response to corrective lenses

AND

 - ii. The patient has had an inadequate response to any other additional, patient appropriate, conservative corrective therapies (e.g. exercises)

AND

 - iii. The patient has good vision in both eyes

- iv. Eye movements are not restricted
- AND**
- v. The patient has small to moderate angle of esotropia
- AND**
- vi. There is a potential for the patient to experience binocular vision

OR

- h. Upper limb spasticity associated with stroke **AND** BOTH of the following:
 - i. The patient has tried physical/occupational therapy, bracing/splinting with inadequate results
 - AND**
 - ii. ONE of the following:
 - 1. The patient has tried and failed ONE conventional prerequisite agent (e.g. benzodiazepine, oral or intrathecal baclofen)
 - OR**
 - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one conventional prerequisite agent

OR

- i. Overactive bladder **AND** ALL of the following:
 - i. The patient has symptoms of urge urinary incontinence, urgency, and frequency
 - AND**
 - ii. Conservative therapies including bladder training, pelvic floor muscle exercises, and fluid management have been inadequate
 - AND**
 - iii. ONE of the following:
 - 1. The patient has tried and failed TWO first line conventional agent prerequisites: Needs to have tried one anticholinergic agent (e.g. oxybutynin, tolterodine, trospium, darifenacin, solifenacin or fesoterodine) **AND** Myrbetriq/mirabegron
 - OR**
 - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH an anticholinergic agent **AND** Myrbetriq/mirabegron

OR

- j. Lower limb spasticity associated with cerebral palsy or stroke **AND** ONE of the following:
 - i. Spasticity is causing pain
 - OR**
 - ii. Spasticity is compromising care or hygiene
 - OR**
 - iii. Spasticity is decreasing the tolerance of other therapies (i.e. orthoses)

OR

- k. Sialorrhea associated with Parkinson's disease **AND** ONE of the following:
 - i. The patient has tried and failed ONE conventional prerequisite agent (e.g. amitriptyline, benztropine, oral hyoscyamine, atropine drops, glycopyrrolate)
 - OR**
 - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ONE conventional prerequisite agent

OR

- l. Another FDA approved indication

AND

- 3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for the requested indication
 - OR**
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or requested duration, whichever is shorter, for all indications except migraine. Approval for migraine is for 6 months.

Renewal Evaluation

1. The patient has been previously approved for the requested agent through the Medical Drug Review Process
AND
2. ONE of the following:
 - a. The patient has a diagnosis of chronic migraine AND treatment with the requested agent has resulted in ALL of the following:
 - i. ONE of the following:
 1. Reduction of 7 or more headache days per month
OR
 2. Reduction of 100 or more headache hours per month from baseline (prior to therapy)
OR
 3. Reduced migraine frequency
OR
 4. Reduced use of acute abortive migraine medication
AND
 - ii. ONE of the following:
 1. The patient is not currently taking a calcitonin gene related peptide (CGRP) agent
OR
 2. The CGRP agent will be discontinued before starting therapy with the requested agent
AND
 - iii. The patient will not be initiating a CGRP agent after starting therapy with the requested agent
AND
 - iv. The prescriber is a headache specialist (e.g. neurologist, The United Council for Neurologic Subspecialties [UCNS] certified) or has consulted with a headache specialist
OR
 - b. The patient has another diagnosis that was approved in initial review AND treatment with the requested agent has resulted in clinical response/improvement from baseline (prior to therapy)
AND
3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the requested duration, whichever is shorter, for all indications

Dysport (abobotulinum toxin A) will be approved when the following are met:

Initial Evaluation

1. The patient does not have any FDA labeled contraindications to the requested agent
AND
2. The patient has ONE of the following diagnoses:

- a. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury) and BOTH of the following:
 - i. The patient's cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck
AND
 - ii. The patient has a history of recurrent involuntary contraction(s) of one or more of the muscles of the neck (e.g. sternocleidomastoid, splenius, trapezius, or posterior cervical muscles)
OR
- b. Lower limb spasticity associated with cerebral palsy, stroke, or post-traumatic brain injury **AND** ONE of the following:
 - i. Spasticity is causing pain
OR
 - ii. Spasticity is compromising care or hygiene
OR
 - iii. Spasticity is decreasing the tolerance of other therapies (i.e. orthoses)
OR
- c. Upper limb spasticity associated with stroke or traumatic brain injury **AND** BOTH of the following:
 - i. The patient has tried physical/occupational therapy or bracing/splinting with inadequate results
AND
 - ii. ONE of the following:
 - 1. The patient has tried and failed ONE conventional prerequisite agent (e.g. benzodiazepine, oral or intrathecal baclofen)
OR
 - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one conventional prerequisite agent
OR
- d. Blepharospasm (including benign essential blepharospasm or VII nerve disorders) **AND** the patient is an adult
OR
- e. Another FDA approved indication

AND

- 3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the requested duration, whichever is shorter

Renewal Evaluation

- 1. The patient has been previously approved for the requested agent through the Medical Drug Review Process
AND
- 2. Treatment with the requested agent has resulted in clinical response/improvement from baseline (prior to therapy)
AND
- 3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR

- b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the requested duration, whichever is shorter, for all indications

Myobloc (rimabotulinum toxin B) will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to the requested agent
AND
2. The patient has ONE of the following diagnoses:
 - a. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury) and BOTH of the following:
 - i. The patient's cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck
AND
 - ii. The patient has a history of recurrent involuntary contraction(s) of one or more of the muscles of the neck (e.g. sternocleidomastoid, splenius, trapezius, or posterior cervical muscles)
OR
 - b. Another FDA approved indication**AND**
3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the duration that is requested, whichever is shorter

Renewal Evaluation

1. The patient has been previously approved for the requested agent through the Medical Drug Review Process
AND
2. The treatment has resulted in a clinical response/improvement from baseline (prior to therapy)
AND
3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the requested duration, whichever is shorter, for all indications

Xeomin (incobotulinum toxin A) will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to therapy
AND
2. The patient has ONE of the following diagnoses:
 - a. Blepharospasm associated with dystonia (including benign essential blepharospasm or VII nerve disorders) **AND** the patient is an adult who was previously treated with onabotulinum toxin A (Botox)
OR
 - b. Cervical dystonia (spasmodic torticollis; applicable whether congenital, due to child birth injury, or traumatic injury) and BOTH of the following:

- i. The patient’s cervical dystonia must be associated with sustained head tilt or abnormal posturing with limited range of motion in the neck
AND
- ii. The patient has a history of recurrent involuntary contraction(s) of one or more of the muscles of the neck (e.g. sternocleidomastoid, splenius, trapezius, or posterior cervical muscles)

OR

- c. Upper limb spasticity associated with stroke **AND** BOTH of the following:
 - i. The patient has tried physical/occupational therapy, bracing/splinting with inadequate results

AND

- ii. ONE of the following:
 - 1. The patient has tried and failed ONE conventional prerequisite agent (e.g. benzodiazepine, oral or intrathecal baclofen)
OR
 - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to one conventional prerequisite agent

OR

- d. Another FDA approved indication

AND

- 3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the duration that is requested, whichever is shorter

Renewal Evaluation

- 1. The patient has been previously approved for the requested agent through the Medical Drug Review Process
AND
- 2. The treatment has resulted in a clinical response/improvement from baseline (prior to therapy)
AND
- 3. ONE of the following:
 - a. The dosing is within FDA labeled dosing for labeled indications or supported in literature for additional indications
OR
 - b. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months or the requested duration, whichever is shorter, for all indications

Agent	Contraindications
Botox	Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation; infection at the proposed injection site; and for detrusor injections, urinary tract infection or urinary retention
Dysport	Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation, allergy to cow’s milk protein, infection at the proposed injection site(s)
Myobloc	Hypersensitivity to any botulinum toxin preparation or to any

	of the components in the formulation; infection at the proposed injection site(s)
Xeomin	Hypersensitivity to the active substance botulinum neurotoxin type A or to any of the excipients; infection at the proposed injection sites

Your health plan does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Your health plan administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in your health plan's administration of plan contracts.

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FDA APPROVED INDICATIONS AND DOSAGE¹⁻⁴

Agent	FDA Labeled Contraindications	Dosing and Administration
<p>Botox® (onabotulinum toxin A)</p>	<ul style="list-style-type: none"> • Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication • Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication • Prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer) • Treatment of spasticity in adult patients • Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain • Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients • Treatment of blepharospasm associated with dystonia in patients ≥ 12 years of age • Treatment of strabismus in patients ≥ 12 years of age <p>Important Limitations: Safety and effectiveness of BOTOX have not been established for:</p> <ul style="list-style-type: none"> • Prophylaxis of episodic migraine (14 headache days or fewer per month) 	<ul style="list-style-type: none"> • Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor • Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor • Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles • Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended • Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles • Cervical Dystonia: Base dosing on the patient’s head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients <ul style="list-style-type: none"> • Axillary Hyperhidrosis: 50 Units per axilla • Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye • Strabismus: The dose is based on prism diopter correction or previous response to treatment

	<ul style="list-style-type: none"> • Treatment of upper or lower limb spasticity in pediatric patients • Treatment of hyperhidrosis in body areas other than axillary 	with BOTOX
Dysport® (abobotulinum toxin A)	<ul style="list-style-type: none"> • Treatment of adults with cervical dystonia • Temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age • Treatment of spasticity in adults • Treatment of lower limb spasticity in pediatric patients 2 years of age and older 	<ul style="list-style-type: none"> • Cervical dystonia: initial dose 500 units IM divided among affected muscles; re-treat every 12 – 16 weeks or long • Glabellar lines: total dose of 50 units IM no more than every 3 months • Spasticity: upper limb 500 Units to 1000 Units; lower limb up to 1500 Units; should not occur in intervals of less than 12 weeks • Lower limb spasticity in pediatric patients: 10 – 15 Units/kg per limb
Myobloc® (rimabotulinum toxin B)	<ul style="list-style-type: none"> • Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia 	Patients previously tolerating botulinum toxin injections: 2,500 to 5,000 units divided among affected muscles
Xeomin® (incobotulinum toxin A)	<p>Treatment or improvement of adult patients with:</p> <ul style="list-style-type: none"> • upper limb spasticity • cervical dystonia • blepharospasm with onabotulinumtoxinA (Botox®) prior treatment • temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity 	<ul style="list-style-type: none"> • Upper Limb Spasticity in Adults: recommended total dose is up to 400 Units no sooner than every 12 weeks • Cervical Dystonia: recommended initial total dose is 120 Units per treatment session • Blepharospasm: base initial dosing on previous dosing for onabotulinumtoxinA (Botox); if not known, the recommended starting dose is 1.25 Units-2.5 Units per injection site • Glabellar Lines: recommended dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each (two injections in each corrugator muscle and one injection in the procerus muscle; wait a minimum of three months before retreatment

Botulinum toxin (BoNT) is a neurotoxin produced by the bacteria *Clostridium botulinum*. Botulinum toxin is divided into 7 structurally similar neurotoxins (type A, B, C [C1, C2], D, E, F, and G) with varying potencies.

BoNT acts by binding presynaptically on cholinergic nerve terminals and decreasing the release of acetylcholine which causes a neuromuscular blockade. It is thought that recovery occurs by the eventual regeneration of the neuromuscular junction.

The potency of BoNT-A is measured in mouse units (MU). One MU is equivalent to the amount of toxin that kills 50% of a group of 20g Swiss-Webster mice within 3 days of intraperitoneal injection (LD50). The minimum lethal dose of BoNT-B in monkeys is 24000 U/kg. Standardization efforts have begun using measurements of the toxin's pharmacologically relevant actions (e.g. median paralysis unit).⁵¹

Safety

Adverse events from the use of botulinum toxin (BoNT) generally fit into one of three general categories; diffusion into neighboring nerves which can lead to unwanted inhibition of those neighboring nerves, continued blockade of signal transmission which is similar to anatomic denervation, or immunoresistance can develop which may result in diminished response to additional injections.¹⁶ Overall the adverse events are localized to the treatment site, transient and related to muscle weakness.³⁸ BoNT products all contain a boxed warning indicating the toxin may spread from the injected area and produce its effects in other areas up to weeks after injection. Life threatening events and death have been reported. The risk is greatest in children treated for spasticity but can occur in adults.³⁴⁻³⁷

Immunogenicity has been reported in some patients treated with BoNT. Antibodies produced against BoNT can reduce the efficacy of BoNT and is dependent on the amount of neurotoxin presented to the immune system. The amount presented to the immune system is different for each product and determined by the agent's specific biological activity and the relationship between that activity and the amount of neurotoxin contained in the preparation. The specific biological activity for the commercially available products is 60 MU-EV/ng, 100 Mu-EV/ng, and 5 MU-EV/ng neurotoxin for Botox, Dysport and Myobloc respectively. The rate of antibody-induced failure of therapy for Botox has been reported at < 1%.⁴⁴

Blepharospasm

Blepharospasm is a type of focal dystonia resulting in involuntary closure of the eyelids. This does not have any effect on a person's vision or mental abilities. Although the cause of blepharospasm is unknown, it is possibly due to the abnormal function of the basal ganglia of the brain.⁶ Several different drug classes have shown some effectiveness in blepharospasm and facial dystonias based upon 3 unproven pharmacologic hypotheses: cholinergic excess, GABA hypofunction, and dopamine excess. Pharmacotherapy is typically less effective than BoNT injections so therefore is considered second line therapy. BoNT injections is regarded as the most effective treatment of choice for the rapid but temporary treatment of orbicularis spasm.⁵

The FDA approval of BoNT for this indication is primarily based on a double-blind comparison of BoNT injection and saline injections, one in each eyelid. Blinded rating showed bilateral reduction in blepharospasm with a greater reduction in the BoNT injected eye. Duration of efficacy lasted approximately 2.5 months. Adverse events were generally mild and included blurred vision, tearing, ptosis, and ecchymosis.

American Academy of Neurology (AAN) guidelines recommend the use of BoNT as a treatment option for blepharospasm while acknowledging the evidence is suboptimal. Due to the large magnitude of benefit seen in the initial trial and lack of other effective therapies, additional evidence in properly controlled clinical trials is unlikely.⁷

Cervical Dystonia

Cervical dystonia (CD) [also called spasmodic torticollis] causes involuntary activation of the muscles of the neck and shoulders resulting in abnormal, sustained, and painful posturing of the head, neck, and shoulders. Data on the use of oral pharmacotherapy is limited. Several studies have shown the efficacy of BoNT in the treatment of CD. One study evaluated the efficacy of BoNT-A compared to trihexyphenidyl

in BoNT treatment naïve patients with CD. BoNT-A was shown to be superior in efficacy as evaluated by the validated Tsui scale with fewer side effects compared to trihexyphenidyl. AAN guidelines conclude that BoNT has longstanding and widespread data in its efficacy and safety for the treatment of CD. BoNT is recommended for the treatment of CD (Level A). Additionally, BoNT is probably more efficacious than trihexyphenidyl (Level B).² EFNS (European Federation of Neurological Societies) guidelines on the diagnosis and treatment of primary dystonias consider BoNT-A a first line therapy for the treatment of primary cranial (excluding oromandibular) or cervical dystonia.¹

Hemifacial Spasm

The muscles of the face are subject to the same movement disorders as other muscle groups (e.g. dystonia, spasticity, and myoclonus). Causes of hemifacial spasms include reduced vascular circulation, facial nerve compression, and lesions in the brain or brainstem caused by diseases like stroke or multiple sclerosis. Secondary causes like trauma or Bell palsy can also cause these spasms.⁴² Treatment options include oral therapies such as carbamazepine, baclofen, and benzodiazepines.^{2,42} Microvascular decompression is also a treatment modality but is limited due to the invasiveness of the procedure.² Hemifacial spasms fall within the category of VII nerve disorder and treatment with BoNT has been evaluated and approved by the FDA.^{2,34}

American Academy of Neurology guidelines consider BoNT a treatment option for hemifacial spasm with a lower level of evidence but BoNT is currently the first treatment choice for most patients.⁴² The guideline also advises that after dose adjustment onabotulinum toxin A and abobotulinum toxin A are probably equivalent in efficacy.³⁴

Hyperhidrosis

Hyperhidrosis (excessive sweating) can be either idiopathic (primary) or secondary to other diseases, medical disorders, medications, or febrile illnesses (e.g. endocrine disorders, neurological disorders, respiratory disease or psychiatric conditions). Incidence is dependent on culture, climate, and a variety of subjective definitions.⁵ Eccrine sweat glands are innervated by the sympathetic nervous system and are responsible for hyperhidrosis. Traditional sweating used to regulate body temperature is controlled by the hypothalamus and emotional sweating is controlled by the cerebral cortex.⁵ Secondary hyperhidrosis typically presents in adults with excessive sweating that occurs both while awake and asleep. Primary hyperhidrosis typically presents in childhood or adolescence and does not occur nocturnally.

Diagnostic criteria consistent with primary hyperhidrosis include excessive sweating of 6 months or more, with 4 or more of the following: primarily involving eccrine-dense (axillae, palms, soles, craniofacial) sites; bilateral and symmetric; absent nocturnally; episodes at least weekly; onset at age ≤ 25 years; positive family history; and impairment of daily activities.⁴

Several topical and systemic agents including iontophoresis (introduction of ionized substances through intact skin by application of a direct current) and botulinum toxin have been used in the treatment of hyperhidrosis. There is limited data on the efficacy of iontophoresis from randomized controlled trials. BoNT has been shown effective for axillary and palmar hyperhidrosis. It requires 20 to 40 injections with a temporary effect which can last anywhere from 3 -7 months and has been shown to cause transient weakness of the small hand muscles.⁵ FDA labeling advises the safety and efficacy of BoNT for hyperhidrosis of other body parts has not been evaluated and use for other body areas are not support by a majority of the compendia.^{30,34} Surgery is also an option but is reserved for a small select patient population. Surgery candidates should have disease onset at < 16 years of age, young at the time of surgery (< 25 years of age), have a BMI < 28 , not have sweating during sleep, be relatively healthy and not have bradycardia.⁵ The most common topical first line agent is Drysol (20% aluminum chloride hexahydrate in absolute anhydrous ethyl alcohol).⁴ Systemic treatment using anticholinergic agents (e.g. glycopyrrolate, propantheline, oxybutynin) may also be used but are limited due to side effects including dry mouth, blurred vision, urinary retention and constipation.^{4,5}

Migraine Prophylaxis

The FDA approval of BoNT for prophylaxis in migraine was based on 2 randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies in patients with chronic migraine who were not on current prophylaxis therapy and had ≥ 15 headache days lasting > 4 hours with $\geq 50\%$ being migraine/probable. The primary efficacy endpoints were change from baseline in frequency and change

from baseline in total cumulative hours of headache on headache days. Both studies showed a statistically significant and clinically meaningful improvement from baseline compared to placebo. EFNS migraine treatment guidelines report good efficacy and tolerability and evidence of efficacy for betablockers, calcium channel blockers, antiepileptic drugs, NSAIDs, antidepressants, and miscellaneous drugs based on empirical data. The guidelines note there is not a commonly accepted indication for starting a patient on a prophylactic regimen but the consensus by the Task Force is that prophylaxis should be discussed with a patient when there is an impact on the quality of life, when business or school attendance is severely impaired, for attacks occurring 2 times a month or greater, for migraines that do not respond to acute treatment, or for migraines with frequent, extended duration, or uncomfortable auras. Successful prophylaxis is a decrease of 50% or greater in the frequency of attacks within 3 months. See appendix for first, second, and third line therapy options (tables 4, 5, and 6).⁶ Additional guidelines also list prophylactic agents based on levels of evidence.⁷ Guidelines do not reference the roll of BoNT in prophylactic therapy.

Neurogenic Bladder

Neurogenic bladder is a condition characterized by detrusor muscle overactivity or underactivity due to neurologic dysfunction or from trauma, disease, or injury. Depending on the site of neurological dysfunction or injury the urinary sphincter may also be affected which could result in urinary incontinence. FDA approval for the use of BoNT in neurogenic bladder was based on 2 double-blind, placebo-controlled, randomized, multi-center trials in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were spontaneously voiding or using catheterization. The primary efficacy endpoint was change from baseline in weekly frequency of incontinence episodes at Week 6. Statistically significant improvements in the primary endpoint versus placebo were seen in both studies with a median duration of treatment effect of 42 to 48 weeks.³⁴

The European Urology Association (EAU) recognizes that anti-muscarinic agents have been the most widely used agents for treating neurogenic detrusor overactivity although these agents are not licensed for this indication in Europe. Non-selective alpha-blockers may be useful in decreasing bladder outlet resistance. Pelvic floor muscle exercises, pelvic floor electro-stimulation, and biofeedback may also be beneficial in select patients. BoNT may be offered as a minimally invasive treatment option with a long-lasting, reversible, chemical denervation.¹⁰ The National Institute of Health and Clinical Excellence (NICE) recommends the botulinum toxin A be offered to patients with spinal cord disease (e.g. spinal cord injury or multiple sclerosis) who have symptoms of overactive bladder and in whom antimuscarinic drugs have proven ineffective or have been poorly tolerated.²⁵

Strabismus

Crossed eyes (strabismus) is a condition in which both eyes do not look at the same place at the same time and is usually caused by poor eye muscle control. Proper eye alignment is important to avoid seeing double, for good depth perception, and to prevent poor vision in the turned eye. This condition typically develops in infants and young children most frequently by age 3. It can develop in older children and adults. Treatment may include eyeglasses, prisms, vision therapy, or eye muscle surgery. When treated early strabismus may be corrected with great results.¹²

FDA approval for BoNT for the treatment of strabismus was based on data from an open label trial of 677 patients treated with one or more BoNT injections. Improvement in alignment was reported in 55% of patients at 6 months or longer following injection.

According to guidelines, patients greater than 3 months experiencing strabismus should be evaluated. Most cases in children are initially treated with glasses. Additional treatment for residual strabismus is usually surgical but other options include prism therapy (e.g. acquired cranial sixth nerve palsy), botulinum toxin (e.g. cranial VI nerve palsy, infantile esotropia) and exercises (e.g. convergence insufficiency, distance esotropia and symptomatic phorias).¹³ Preferred Practice Patterns from the American Academy of Ophthalmology provide several treatment modalities that may be used alone or in combination to correct strabismus, these include correction of refractive errors, bifocals, prism therapy, amblyopia treatment, extraocular muscle surgery, and botulinum toxin A injection. These preferred practice patterns recommend surgery only when more conservative methods (e.g. glasses) have failed or are unlikely to be of benefit. The use of BoNT is recommended as an alternative to surgery in selected patients but its value in infantile esotropia is not clearly established. Its use should be reserved for those

with good vision in each eye, absence of restricted eye movement, a small to moderate angle of esotropia, and potential for binocular vision. Disadvantages of this therapy are frequent repeated injections and need for general anesthesia.¹⁴

Upper Limb Spasticity

Spasticity is an increase in muscle tone due to hyperexcitability of the stretch reflex and is characterized by a velocity-dependent increase in tonic stretch reflexes. The exact incidence is unknown but likely affects over half a million people in the U.S. alone. Oral therapies such as benzodiazepines, baclofen, dantrolene, and tizanidine may be very effective but can have unwanted side effects such as changes in mood, cognition and sedation.¹⁵

Several randomized, multi-center, double-blind, placebo-controlled pivotal trials have evaluated the safety and efficacy of BoNT in the treatment of patients with upper limb spasticity who were at least 6 months post stroke. In Study 1 patients were assigned a baseline Ashworth score (the Ashworth Scale is a clinical measure of the force required to move an extremity around a joint). The primary efficacy endpoint was wrist flexors muscle tone at week 6, as determined by the Ashworth score. Scores on the Ashworth scale range from 0 (no increase in muscle tone) to 4 (limb rigid in flexion or extension [very severe]). Mean changes from baseline in wrist flexor muscle tone were reported for 126 patients but a statistically significant p value was not reported. Study 2 had the same efficacy endpoint but evaluated 3 doses of BoNT. Study 3 evaluated 3 doses of BoNT but the primary efficacy endpoint was wrist and elbow flexor tone as measured by the same scale noted above. Mean change from baseline values were reported for all studies but discussions on the clinical and statistical significance were not reported. The assumption is that all primary efficacy endpoints were significant as these studies were evaluated for FDA approval. A fourth multi-center, prospective, double blind, randomized, and placebo controlled study evaluated the safety and efficacy of Dysport in adults with upper limb spasticity. The trial had 243 subjects who were randomized to treatment with Dysport 500 units (n=80), Dysport 1000 units (n=79), or placebo (n=79). The primary outcome measure was intensity of muscle tone rated by Modified Ashworth Scale.

American Academy of Neurology guidelines recognize physical and occupational therapy, bracing/splinting, tizanidine, benzodiazepines, oral or intrathecal baclofen, tendon release, rhizotomy and BoNT as treatment options for upper limb spasticity. These guidelines further recommend that BoNT be offered as a treatment option understanding there isn't controlled trials comparing BoNT to other treatment modalities for spasticity.¹⁶

Overactive Bladder

The International Continence Society defines overactive bladder (OAB) as the presence of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of UTI or other obvious pathology. Therefore, OAB symptoms consist of four components: urgency, frequency, nocturia and urgency incontinence."⁹

BoNT was FDA approved for the treatment of overactive bladder based on 2 double-blind, placebo-controlled, randomized, multicenter 24 week trials in patients with OAB and symptoms of urge urinary incontinence, and frequency. Patients had to have at least 3 urinary incontinence episodes and at least 24 micturitions in 3 days. Patients received 20 injections into the detrusor muscle. The primary efficacy endpoint was change from baseline in daily frequency or urinary incontinence episodes. Both studies showed a statistically significant improvement compared to placebo.

European Association of Urology (EAU) urinary incontinence guidelines, the American Urology Association guidelines (AUA), and Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) recommend behavior modification such as bladder training, pelvic floor muscle exercises, and fluid management as first line therapy for all patients. The use of anti-muscarinic or oral β_3 -adrenoceptor agonists medications may be added to behavior therapy. Both agencies also recommend onabotulinumtoxinA intradetrusor injections in those with urge urinary incontinence refractory to behavioral therapy and pharmacologic therapy.^{8,9}

Compendia Supported Indications

Botulinum toxin is an agent that has been available for many years, available in different forms and by different manufacturers with varying uses. It is recognized there is a host of primary literature available including both product and indication specific information.

For the purposes of the criteria, indications deemed appropriate are those that are supported by at least two compendia where one of the compendia is DrugDex with a level of evidence of 2B and strength of recommendation of B or supported in guidelines with highest level of evidence recommendation.

Achalasia

Achalasia is an esophageal motility disorder characterized by the absence of esophageal peristalsis and impaired lower esophageal sphincter (LES) relaxation in response to swallowing. The abnormality causes a functional obstruction at the gastroesophageal junction. Incidence in the United States is approximately 1 in 100,000 people per year and typically occurs in patients between 25 and 60 years of age. The goal of therapy is to relieve the symptoms by eliminating the outflow resistance caused by the non-relaxing LES. The American College of Gastroenterology (ACG) guidelines on management of achalasia recommend either graded pneumatic dilation (PD) or laparoscopic surgical (myotomy) as initial therapy for those fit and willing to undergo surgery.²⁰ ACG recommend botulinum toxin therapy for patients who are not good candidates for more definitive therapy with PD or surgical myotomy. According to ACG, oral pharmacologic therapies (e.g. calcium channel blockers, long acting nitrates) are the least effective treatment options for achalasia.²⁰

Chronic Anal Fissure

Anal fissure is a linear tear or crack in the anal canal involving the epithelium in the short term but the full thickness of the mucosa in the long term. It is thought that early on these fissures begin with trauma from passage of hard or painful bowel movements. Most people heal small tears without long term issues but in patients with abnormalities of the anal sphincter the small tears can progress to acute and chronic fissures. Sphincter abnormalities more commonly seen involve hypertonicity and hypertrophy which can lead to an increase in anal canal and sphincter resting pressures.⁵⁰

Non-invasive first and second line therapy typically consists of switching to a high fiber diet, adding bulking agents, laxatives as needed to maintain regular bowel movements, sitz baths that can provide pain relief, and intra-anal 0.4% nitroglycerin. Recurrence rates are fairly high (30 to 70%) especially in patients that do not maintain a high fiber diet. BoNT has shown efficacy for the treatment of acute and chronic fissures with effects lasting approximately 3 months.^{48,49} For patients who continue to experience fissures (chronic), lateral internal sphincterotomy has been the gold standard treatment but drawbacks of this therapy include potential gas, mucus, or occasional stool incontinence.

Spasticity

Cerebral palsy (CP) is a generalized term for a group of disorders affecting body movement, balance, and posture that is caused by abnormal development or damage to one or more sections of the brain that control muscle tone and motor activity. Patients are typically born with this condition but it can also be due to brain damage from an accident, fall, or child abuse. Symptoms usually appear by age 3 and vary from very mild to very profound. The most common signs include lack of muscle coordination when performing voluntary movements; stiff or tight muscles and exaggerated reflexes (spasticity); walking with one foot dragging, walking on the toes or a scissored gait. There isn't a cure for CP but available therapy can reduce the disabilities associated with CP. Treatment is patient specific and involves a multi-disciplinary care team.²¹

The American Academy of Neurology published 2 guidelines supporting the use of BoNT in the treatment of CP patients with spasticity that warrants therapy.^{16,22} It is common practice to use BoNT-A in combination with serial casting, orthoses, and physical and occupational therapy in this patient population.¹⁶ European consensus guidelines also recommend BoNT as a treatment option for patients with focal and multi-focal spasticity. See Gross Motor Function Classification System and CP Treatment Modalities in appendix.²³

The National Institute for Health and Clinical Efficacy (NICE) guidelines recommends the use of botulinum toxin A as a treatment option in patients with focal spasticity of the upper and lower limb that is impeding

fine or gross motor function, compromising care and hygiene, impeding tolerance of other treatments (e.g. orthoses) or causing pain.²⁴

Types of spasticity due to other neurologic conditions or neurological injury where BoNT has shown efficacy include stroke, multiple sclerosis, injury of the brain or spine from either disease or trauma, spastic hemiplegia, hereditary spastic paraplegia, and Schilder's disease. Additional agents such as baclofen, benzodiazepines as well as physical and/or occupational therapy may also improve symptoms.^{46,47}

Focal Limb Dystonia

Focal limb dystonia is a movement disorder that affects the arms and/or legs. It causes cramping and posturing of the elbows, hands, and fingers that lead to the inability to perform certain occupational tasks. Onset is typically between 10 and 50 years of age. The term focal limb dystonia includes focal hand dystonia also known as "writer's cramp". Physical therapy, slow stretching, and physical modalities (e.g. ultrasonography, biofeedback) are sometimes helpful for focal or regional dystonias. Systemic therapies benefit about one third of patients and include several options including cholinergics, benzodiazepines, antiparkinsonism agents, anticonvulsants, baclofen, carbamazepine, and lithium. Successful drug therapy often uses a combination of medications. BoNT or phenol/alcohol injections are powerful tools in improving symptoms in these patients.¹⁷ Clinical evidence for the efficacy of the use of BoNT in focal limb dystonia primarily focuses on the upper extremities although some studies did include patients with lower limb dystonia. A randomized, double-blind trial of 40 patients with writer's cramp treated patients with either BoNT or saline with a single injection. If inadequate or no response was seen patients were allowed a second injection after 1 month. The primary efficacy endpoint was subjective (desire to continue injections). The majority of patients (70%) elected to continue.²

Guidelines from the American Academy of Neurology recommend BoNT as a treatment option for patients with focal limb dystonia and consider it probably effective.² European guidelines recommend BoNT A as a first line choice for the treatment of most types of focal dystonia.¹ Benefits of BoNT therapy can last 3 to 6 months.³⁸

Oromandibular Dystonia

Oromandibular dystonia is a focal dystonia characterized by forceful contractions of the face, jaw, and/or tongue which causes difficulty in opening or closing of the jaw as well as affecting chewing, swallowing, or speech. Sometimes it is referred to as cranial dystonia which is a more broad term for dystonias affecting any part of the head. Onset is typically later in life, between 40 and 70 years of age, and seems to be more common in women than in men. Estimated prevalence is 68.9 cases per one million in the United States.⁴¹ Oromandibular dystonia is either primary (only apparent neurologic disorder) or secondary (due to causes such as drug exposure or disorders like Wilson's disease). There is currently no specific diagnostic test to confirm the diagnosis. While treatment is typically customized to the individual, about one third of patients show benefit in symptoms when treated with oral agents such as clonazepam, trihexyphenidyl, diazepam, tetrabenazine, and baclofen. The use of BoNT has shown some efficacy in approximately 70% of patients and appears to be most effective in jaw-closure dystonia.²⁶

EFNS guidelines on primary dystonias recommend BoNT A as a first line treatment for primary cranial dystonia but exclude oromandibular from review.¹ The rationale for this exclusion is unclear however multiple compendia support the use of BoNT for the treatment of oromandibular dystonia.^{31,40} Treatment effects generally last 3 to 4 months.³⁸

Sialorrhea (Excessive Salivation)

Sialorrhea (drooling) is a significant disability for a large number of patients with cerebral palsy and for a small number of patients with other types of neurologic or cognitive impairment. In patients with cerebral palsy drooling causes social, psychological and clinical burdens on the patient and caregivers. Approximately 10-37% of patients with cerebral palsy report having issues with drooling due to neurologic impairment. Medical or aggressive physical management are recommended prior to considering surgical interventions. Based on the noninvasive nature and degrees of response (although data is unable to confirm efficacy), all patients capable of oral motor training should undergo at least a 6 month trial prior to a surgical intervention. Anticholinergics have been used but the doses tolerated have not completely ceased drooling and side effects may make these agents difficult to tolerate. Data has shown a 50%

decrease in drooling for patients given benztropine while glycopyrrolate has shown a decrease in drooling in 95% of patients but these data should be interpreted with caution based on the quality of the studies. Additional data has shown the use of BoNT providing efficacy and lasting for months.²⁷ EFNS guidelines on the treatment of sialorrhea due to amyotrophic lateral sclerosis (ALS) recommend treatment for sialorrhea with oral hyoscine, atropine drops, glycopyrrolate or amitriptyline. BoNT may be tried but long-term efficacy and safety data were not available and the intervention was deemed experimental.²⁹

A review published in the European Journal of Neurology concluded that in general BoNT can be used to improve sialorrhea in patients with Parkinson disease, parkinsonian syndromes, motor neuron disease and cerebral palsy despite some limitations of the evaluated studies.²⁸ The use of BoNT for the treatment of excessive salivation (sialorrhea) is supported by multiple compendia.^{30,31,40} Efficacy can last from a few weeks to a few months.²⁸

Lower Urinary Tract Symptoms due to Benign Prostate Hyperplasia (BPH)

Cellular accumulation in benign prostatic hyperplasia may result from epithelial proliferation. The hyperplasia is thought to result in enlargement of the prostate that can restrict urine flow from the bladder. The voiding dysfunction that results from the enlargement and bladder outlet obstruction (BOO) is also referred to as lower urinary tract symptoms (LUTS). There is overlap such that not all men with BPH have LUTS and not all men with LUTS have BPH although half of men diagnosed with histopathologic BPH have moderate to severe LUTS. Patients with LUTS exhibit urinary frequency, urgency, nocturia, decreased or intermittent force of stream or sensations of incomplete emptying. It is estimated that approximately 50% of men have histopathologic BPH by age 60. Patients with mild LUTS can be treated with medical therapy. Transurethral resection of the prostate (TURP) is accepted as the standard for relieving BOO secondary to BPH but the majority of patients present with more mild LUTS and can receive medical therapy.³²

Alpha1 blockers are often the first line therapy for LUTS due to a rapid onset of action and good efficacy. These agents all have similar efficacy and safety. 5α-reductase inhibitors should only be used in men with bothersome moderate-to-severe LUTS and enlarged prostates or elevated PSA. Surgery is typically required for patients with refractory or recurrent urinary retention, overflow incontinence, urinary tract infections, bladder stones, or dilatation of the upper urinary tract due to obstruction or when other more conservative measure have provided insufficient relief. The EAU guidelines consider ethanol and BoNT injections to be experimental; however this indication is supported in at least 2 compendia.^{31,33,40}

Additional Dystonias

In general, dystonia is an uncontrollable repeated or twisting movement from muscle contraction that can affect several areas of the body. Symptoms can range from mild to severe and debilitating affecting the ability to perform activities of daily living. There isn't a cure for dystonia but treatment options such as BoNT as well as oral medications such as levodopa, carbidopa, tetrabenazine, trihexyphenidyl, benztropine, benzodiazepines, or baclofen may help in early onset of symptoms. Specific types of dystonia not already covered in greater detail where BoNT has shown efficacy include laryngeal (spasmodic dysphonia) and torsion dystonia (both acquired and idiopathic).⁴⁵

FDA Labeled Indications	Botox	Dysport	Myobloc	Xeomin
	onabotulinum toxin A ³⁴	abobotulinum toxin A ³⁵	rimabotulinum toxin B ³⁶	incobotulinum toxin A ³⁷
Blepharospasm	Recommended initial dose is 1.25 to 2.5 units ^e			Recommended initial dose should be same as onabotulinum toxin A ⁱ max 35 units/eye ^b
Cervical dystonia	Patient specific dosing 198-400 units divided among selected	Recommended initial dose 500 units ^{b,g}	Recommended dose 2,500 to 5,000 units divided among	Recommended dose is 120 units ^b

	muscles ^{c,d}		selected muscles ^h	
Primary axillary hyperhidrosis	Recommended dose is 50 units per axilla			
Chronic Migraine prophylaxis	Recommended dose is 155 units ^b			
Detrusor Overactivity associated with a Neurologic condition	Recommended and max dose is 200 units ^a			
Overactive bladder	Recommended and max dose is 100 units ^a			
Strabismus	Recommended initial dose ranges from 1.25 to 5 units depending on prism diopters ^f			
Upper limb spasticity	Patient specific dosing 75-400 units divided among selected muscles ^{b,c}	1 to 2 injection(s) per muscle at a dose of 100 – 400 units ^m . Patients may require up 500 – 1000 units to respond		1 to 4 injection sites per muscle at a dose of 5 to 200 Units depending on muscle type- no sooner than every 12 weeks
OFF label indications	Botox	Dysport	Myobloc	Xeomin
	onabotulinum toxin A	abobotulinum toxin A	rimabotulinum toxin B	incobotulinum toxin A
Achalasia ^{30,31}	^j 20-25 units injected into each of 4 quadrants for a total of 80-100 units ^{20,31,40}			
Chronic Anal Fissure	10 units injected into each side of the fissure (20 units total into internal sphincter) ⁴⁸			
Cerebral Palsy (spasticity) ^{30,31}	Up to 200 units per treatment ³⁰⁻³¹	^k 24 – 30 units/kg ^{16,38}		
Focal limb dystonia ^{1,2,40}	^l 5-20 units for small muscles and muscles of forearm. ³⁸			
Laryngeal dystonia	1.25-25 units ³¹			

(spasmodic dysphonia) ^{31,40}				
Oromandibular dystonia ^{31,40}	2-100 units in each muscle ^{38,40}		30-100 units divided among selected muscles ⁴¹	
Sialorrhea ^{30,31}	5-100 units (per side) parotid gland 5-30 units (per side) submandibular gland ^{28,30,31}		1000 units (per side) parotid gland 250 units (per side) submandibular ²⁸	
Torsion Dystonia	140 units ⁵² (customized to patient)			
Lower Urinary Tract Symptoms (LUTS) ^{31,40}	50-100 units ³⁹			
Hemifacial spasm ^{31,40}	12 to 25 units divided among selected muscles ^{31,40}	28 to 220 units divided among selected muscles ³¹		

a-reinjection no sooner than 12 weeks from prior bladder injection

b-recommended re-treatment schedule is every 12 weeks

c-dosing range from clinical trials

d-in trials, effect lasted approximately 3 months for most patients

e-cumulative dose in 30 days should not exceed 200 units. Effects generally last 3 months.

f-maximum single injection for any one muscle is 25 units. Evaluate dose efficacy in 7-14 days.

g-reducing dose injected into sternocleidomastoid muscle may reduce dysphagia. Total single treatment dose should be between 250 and 1000 units. Doses above 1000 units not evaluated.

h-in patients with a prior history of tolerating BoNT. Use lower initial dose for treatment naïve. Duration of effect lasted 12-16 weeks at doses of 5,000 to 10,000 units in clinical trials.

i-if Botox dose unknown, initial dose should be between 1.25 and 2.5 units/injection site. Dose should not exceed 70 units (35 units/eye).

j-symptoms typically reappear after 6 months (50% of patients)²⁰

k-total dose is 120 units per treatment session, higher doses do not provide additional efficacy.³⁸

l-subsequent injections should be given at 2-4 month intervals

m- re-treat every 12 to 16 weeks or longer as needed based on response with doses between 500 – 1000 units

BoNT preparations are not interchangeable and dosing units cannot be compared or converted into units of other preparations. For Botox, when treating adults for one or more indications, the maximum cumulative dose should not exceed 400 units in a 3 month interval.³⁴

Patients with bladder dysfunction (e.g. overactive bladder, urinary incontinence, neurogenic bladder) should be free of a urinary tract infection (UTI) and be treated with prophylactic antibiotics (except aminoglycosides) 1-3 days prior to injection, on BoNT treatment day, and for 1-3 days post treatment to decrease the risk of a procedure related UTI.³⁴

Dosing information listed for off label indications are based on available evidence therefore variations in dosing may be applicable.

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Your health plan does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Your health plan administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in your health plan's administration of plan contracts.

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