Drug and Biologic Coverage Policy

Effective Date **3/1/2023**
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Coverage Policy Number **1106**

Botulinum Therapy

Table of Contents

Related Coverage Resources

Calcitonin Gene-Related Peptide (CGRP) Inhibitors
Hyperhidrosis Treatments

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

This policy addresses coverage criteria for the following products:

- abobotulinumtoxinA **(Dysport®)**
- incobotulinumtoxinA **(Xeomin®)**
- onabotulinumtoxinA **(Botox®)**

NOTE: The three botulinum therapies are NOT interchangeable with one another and are only approved for use as listed in the criteria below.

Each of the three (3) botulinum therapies are considered medically necessary for the following drug specific conditions and criteria below:

NEUROLOGIC

Condition	Product	Criteria for Use
Blepharospasm	**Botox** **Dysport** **Xeomin**	BOTH of the following: • Treatment for blepharospasm characterized by intermittent or sustained closure of the eyelids caused by involuntary contractions of the orbicularis oculi muscle

Condition	Product	Criteria for Use
		• Prescribed by, or in consultation with, a neurologist or ophthalmologist

Cervical dystonia (including spasmodic torticollis)	**Botox Dysport Xeomin**	Treatment when ALL of the following are present:
		• Documentation of both of the following:
		  ○ Involuntary, simultaneous activation of agonist and antagonist muscles of the neck and shoulder (for example, sternocleidomastoid, splenius, levator scapulae, trapezius, semispinalis, scalene)
		  ○ Sustained head torsion and/or tilt with limited range of motion in the neck
		• Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist or a physical medicine and rehabilitation physician

Prevention of Chronic Migraine Headache	**Botox**	Initial Authorization Criteria
		ALL of the following are met:
		• Age 18 years or older
		• Diagnosis of chronic migraine headache as defined by 15 days or more per month with headache lasting four hours a day or longer
		• Documentation of ONE of the following:
		  ○ Failure following a minimum 8 week trial of TWO migraine prevention therapies from different classes of medications including the following:
		  ▪ Angiotensin receptor blockers or angiotensin converting enzyme inhibitors
		  ▪ Antidepressants
		  ▪ Antiepileptic drugs
		  ▪ Beta-blockers
		  ○ Contraindication or intolerance to **ALL** of the following: angiotensin receptor blockers/angiotensin converting enzyme inhibitors, antidepressants, antiepileptic drugs, and beta-blockers
		• Prescribed by, or in consultation with, a board certified pain management specialist, neurologist, or otolaryngologist
		
		Reauthorization Criteria
		OnabotulinumtoxinA (Botox) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response (for example, reduction in monthly migraine days or hours or reduction in days requiring acute migraine-specific treatment from the time that Botox was started).

Essential tremor	**Botox**	BOTH of the following: • Treatment of disabling condition (including head, neck, hand, and voice tremor) • Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist or a physical medicine and rehabilitation physician

Focal dystonias	**Botox**	BOTH of the following:
		• Treatment for any the following:
		  ○ Focal hand dystonia (for example, writer's cramp) causing persistent pain or interfering with the ability to perform age-related activities of daily living
		  ○ Adductor spasmodic dysphonia/laryngeal dystonia
		  ○ Jaw-closing oromandibular dystonia
		  ○ Meige's syndrome/cranial dystonia (i.e., blepharospasm)

Condition	Product	Criteria for Use
		• Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist, otolarnygologist or a physical medicine and rehabilitation physician
Spasms/palsies	**Botox**	BOTH of the following: • Treatment for any the following: o Hemifacial spasms o Seventh cranial nerve palsy (Bell's Palsy) o Gaze palsies causing persistent pain or vision impairment • Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist or a physical medicine and rehabilitation physician
Spasticity	**Botox**	BOTH of the following: • Treatment for any the following: o Cerebral palsy (including spastic equinus foot deformities) o Localized adductor muscle spasticity in multiple sclerosis o Spinal cord injury o Traumatic brain injury o Hereditary spastic paraplegia o Lower limb spasticity with documentation of significant decrease of function or Activities of Daily Living (for example, walking) in pediatric or adult individuals o Upper limb spasticity with documented significant decrease of function or Activities of Daily Living (for example, washing, eating) in pediatric or adult individuals • Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist or a physical medicine and rehabilitation physician
	Dysport	BOTH of the following: • Treatment for any the following: o Cerebral palsy (including spastic equinus foot deformities) o Spasticity in multiple sclerosis o Lower limb spasticity with documentation of significant decrease of function or Activities of Daily Living (for example, walking) in pediatric or adult individuals o Upper limb spasticity with documented significant decrease of function or Activities of Daily Living (for example, washing, eating) in pediatric or adult individuals • Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist or a physical medicine and rehabilitation physician
	Xeomin	BOTH of the following: • Treatment for any the following: o Lower limb spasticity with documentation of significant decrease of function or Activities of Daily Living (for example, walking) in pediatric or adult individuals o Upper limb spasticity with documented significant decrease of function or Activities of Daily Living (for example, washing, eating) in pediatric or adult individuals • Prescribed by, or in consultation with, a board certified pain management specialist, a neurologist or a physical medicine and rehabilitation physician

GASTROINTESTINAL

Condition	Product	Criteria for Use
Chronic anal fissure	**Botox**	BOTH of the following: • Treatment following failure of conventional non-surgical treatment (for example, nitrate preparations, sitz baths, stool softeners, bulk agents, diet modifications) • Prescribed by, or in consultation with, a gastroenterologist or a surgeon
Hirschsprung disease	**Botox** **Dysport**	BOTH of the following: • Treatment of obstructive symptoms due to a non-relaxing internal anal sphincter following surgery for Hirschsprung disease • Prescribed by, or in consultation with, a gastroenterologist or a surgeon
Primary esophageal achalasia	**Botox**	BOTH of the following: • Treatment with any of the following: o Concomitant illness and/or high risk for complications from myotomy or dilation o Poor response to prior myotomy or dilation o History of perforation caused by previous pneumatic dilation o Epiphrenic diverticulum • Prescribed by, or in consultation with, a gastroenterologist

EXOCRINE

Condition	Product	Criteria for Use
Glandular secretion	**Botox**	BOTH of the following: • Treatment of cholinergic-mediated secretions associated with a fistula (for example, parotid gland, pharyngocutaneous) refractory to pharmacotherapy (including anticholinergics) • Prescribed by, or in consultation with, a dermatologist, an endocrinologist, a neurologist or an otolaryngologist
Sialorrhea resulting from Cerebral Palsy	**Botox**	BOTH of the following: • Documented failure / inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE of the following: o Atropine o Glycopyrolate • Prescribed by, or in consultation with, an endocrinologist, a neurologist or an otolaryngologist
Sialorrhea resulting from Parkinsonism	**Botox**	BOTH of the following: • Documented failure / inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE of the following: o Glycopyrolate o Scopolamine • Prescribed by, or in consultation with, an endocrinologist, a neurologist or an otolaryngologist
Chronic Sialorrhea	**Xeomin**	Prescribed by, or in consultation with, a neurologist or an otolaryngologist
Hyperhidrosis	**Botox**	Treatment for ANY of the following when the associated criteria are met: • Primary axillary hyperhidrosis inadequately managed with a prescription topical agent and BOTH of the following: o ONE of the following: ▪ The condition is significantly interfering with the ability to perform age-appropriate activities of daily living ▪ The condition is causing persistent or chronic cutaneous conditions such as skin maceration, dermatitis, fungal infections and secondary microbial conditions o Prescribed by, or in consultation with, a dermatologist, an endocrinologist or a neurologist

Condition	Product	Criteria for Use
		• Palmar hyperhidrosis refractory to conventional medical treatment including both topical and systemic pharmacotherapy (unless clinically contraindicated) and BOTH of the following: o ONE of the following: ▪ The condition is significantly interfering with the ability to perform age-appropriate activities of daily living ▪ The condition is causing persistent or chronic cutaneous conditions such as skin maceration, dermatitis, fungal infections and secondary microbial conditions o Prescribed by, or in consultation with, a dermatologist, an endocrinologist or a neurologist • Gustatory sweating (Frey's syndrome, diabetic gustatory sweating) and the following: o Prescribed by, or in consultation with, a dermatologist, an endocrinologist or a neurologist

OPHTHALMOLOGIC

Condition	Product	Criteria for Use
Strabismus disorders in adults	**Botox**	ALL of the following: • Treatment when any of the following is present: o Horizontal strabismus up to 50 prism diopters o Vertical strabismus o Persistent sixth nerve palsy of one month or longer duration WITH ANY of the following: ▪ Diplopia ▪ Impaired depth perception ▪ Impaired peripheral vision ▪ Impaired ability to maintain fusion • Prescribed by, or in consultation with, a neurologist or ophthalmologist
Strabismus disorders in children	**Botox**	BOTH of the following: • Treatment to achieve normal binocular motor alignment • Prescribed by, or in consultation with, a neurologist or ophthalmologist

UROLOGIC

Condition	Product	Criteria for Use
Bladder dysfunction	**Botox**	BOTH of the following: • Treatment of ONE of the following: o Overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of a trial of two agents from either of the following classes: anticholinergic medications (for example, darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium) OR beta-3 adrenergic agonists* (for example, Myrbetriq, Gemtesa) o Urinary incontinence due to detrusor overactivity in adults who have an inadequate response to or are intolerant of an anticholinergic medication (for example, darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium) OR a beta-3 adrenergic agonist* (for example, Myrbetriq, Gemtesa) when associated with any of the following: ▪ Multiple sclerosis (MS) ▪ Spina bifida

Condition	Product	Criteria for Use
		▪ Spinal cord injury (SCI) ▪ Intracranial lesion or cerebrovascular accident (CVA) o Neurogenic detrusor overactivity (NDO) in pediatric individuals age 5 years or older who have an inadequate response to or are intolerant of an anticholinergic medication OR a beta-3 adrenergic agonist. o Interstitial cystitis/bladder pain syndrome when there is an inadequate response to other second- and third-line treatment options (for example, oral or intravesical treatments and cystoscopy) • Prescribed by, or in consultation with, a urologist or gynecologist *May require prior authorization

The botulinum therapy products are considered not medically necessary for all other indications including the following:

- Cosmetic purposes

Initial authorization is up to four (4) treatments in a 12 month period (one [1] treatment every 90 days).

If the initial approval criteria (listed above) are met AND clinical improvement with previous Botulinum Therapy is documented but duration of benefit is less than 90 days/treatment, then up to six treatments in a 12 month period (one treatment per 60 days) may be considered on a case-by-case basis.

Botulinum Therapy is considered medically necessary for continued use when the following are met:

- Initial criteria are met
- Documentation of a positive clinical response

Reauthorization for up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Botulinum Therapy is considered experimental, investigational or unproven for ANY other use including the following:

- Bruxism
- Chronic low back pain
- Gastroparesis
- Headache including:
  - Cervicogenic headache
  - Chronic daily headache
  - Episodic migraine headache (i.e., 14 headache days or fewer per month)
  - Menstrual headache (for example, 90% of attacks generally occur between two days before menses and the last day of menses)
  - Tension-type headache
- Hemorrhoid pain
- Lateral epicondylitis
- Nausea and vomiting, post sleeve gastrectomy
- Myofascial pain
- Plantar Hyperhidrosis
- Spastic pelvic floor syndrome
- Sphincter of Oddi dysfunction

- Temporomandibular joint (TMJ) syndrome
- Tics
- Trigeminal Neuralgia
- Voiding dysfunction associated with benign prostatic hyperplasia

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication

Brand Name	Approved Indication
Botox	**Bladder Dysfunction** *Overactive Bladder* Botox (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication. *Detrusor Overactivity associated with a Neurologic Condition* Botox is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication. *Pediatric Detrusor Overactivity associated with a Neurologic Condition* Botox is indicated the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication. **Chronic Migraine** Botox is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer). *Limitations of Use* Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies. **Spasticity** Botox is indicated for the treatment of spasticity in patients 2 years of age and older. *Limitations of Use* Botox has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. **Cervical Dystonia** Botox is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia. **Primary Axillary Hyperhidrosis** Botox is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. *Limitations of Use* The safety and effectiveness of Botox for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive Botox for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid

Brand Name	Approved Indication
	symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease. Safety and effectiveness of Botox have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18. **Blepharospasm and Strabismus** Botox is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older. **Botox Cosmetic** is also available and is indicated for the following: Glabellar Lines Botox Cosmetic (onabotulinumtoxinA) is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Lateral Canthal Lines Botox Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients. Forehead Lines Botox Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe forehead lines associated with frontalis muscle activity in adult patients.
Dysport	**Cervical Dystonia** Dysport is indicated for the treatment of cervical dystonia in adults. **Glabellar Lines** Dysport is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients less than 65 years of age. **Spasticity** Dysport is indicated for the treatment of spasticity in patients 2 years of age and older.
Xeomin	**Blepharospasm** Xeomin is indicated for the treatment of blepharospasmin adult patients. **Cervical Dystonia** Xeomin is indicated for the treatment of cervical dystonia in adult patients. **Chronic Sialorrhea** Xeomin is indicated for the treatment of chronic sialorrhea in patients 2 years of age and older. **Glabellar Lines** Xeomin is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. **Upper Limb Spasticity** Xeomin is indicated for the treatment of upper limb spasticity in adult and pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy.

Recommended Dosing

FDA Recommended Dosing

<table>
<tr><th>Brand</th><th>Recommended Dosing</th></tr>
<tr><td>Botox</td><td>
**Refer to the prescribing information (product label) for complete dosing information.

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3-month interval. In pediatric patients, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval.
Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor.
Adult 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
Pediatric Detrusor Overactivity associated with a Neurologic Condition: 0.5 mL injections across 20 sites into the detrusor.

Greater than or equal to 34 kg: Recommended total dose is 200 Units
Less than 34 kg: Recommended total dose is 6 Units/kg

Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles
Adult Upper Limb Spasticity: In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see table below) at a given treatment session.

Botox Dosing by Muscle for Adult Upper Limb Spasticity
<table>
<tr><th>Muscle</th><th>Recommended Dose
Total Dosage (Number of Sites)</th></tr>
<tr><td>Biceps Brachii</td><td>60 Units to 200 Units divided in 2 to 4 sites</td></tr>
<tr><td>Brachioradialis</td><td>45 Units to 75 Units divided in 1 to 2 sites</td></tr>
<tr><td>Brachialis</td><td>30 Units to 50 Units divided in 1 to 2 sites</td></tr>
<tr><td>Pronator Teres</td><td>15 Units to 25 Units in 1 site</td></tr>
<tr><td>Pronator Quadratus</td><td>10 Units to 50 Units in 1 site</td></tr>
<tr><td>Flexor Carpi Radialis</td><td>12.5 Units to 50 Units in 1 site</td></tr>
<tr><td>Flexor Carpi Ulnaris</td><td>12.5 Units to 50 Units in 1 site</td></tr>
<tr><td>Flexor Digitorum Profundus</td><td>30 Units to 50 Units in 1 site</td></tr>
<tr><td>Flexor Digitorum Sublimis</td><td>30 Units to 50 Units in 1 site</td></tr>
<tr><td>Lumbricals/Interossei</td><td>5 Units to 10 Units in 1 site</td></tr>
<tr><td>Adductor Pollicis</td><td>20 Units in 1 site</td></tr>
<tr><td>Flexor Pollicis Longus</td><td>20 Units in 1 site</td></tr>
<tr><td>Flexor pollicis brevis/ Opponens pollicis</td><td>5 Units to 25 Units in 1 site</td></tr>
</table>

Adult Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see table below).

Botox Dosing by Muscle for Adult Lower Limb Spasticity
<table>
<tr><th>Muscle</th><th>Recommended Dose
Total Dosage (Number of Sites)</th></tr>
<tr><td>Gastrocnemius medial head</td><td>75 Units divided in 3 sites</td></tr>
<tr><td>Gastrocnemius lateral head</td><td>75 Units divided in 3 sites</td></tr>
<tr><td>Soleus</td><td>75 Units divided in 3 sites</td></tr>
<tr><td>Tibialis Posterior</td><td>75 Units divided in 3 sites</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Brand</th><th>Recommended Dosing</th></tr>
<tr><td></td><td>
<table>
<tr><td>Flexor hallucis longus</td><td>50 Units divided in 2 sites</td></tr>
<tr><td>Flexor digitorum longus</td><td>50 Units divided in 2 sites</td></tr>
</table>

Pediatric Upper Limb Spasticity: When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval. The recommended dose for treating pediatric upper limb spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles. The total dose of Botox administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower.

Botox Dosing by Muscle for Pediatric Upper Limb Spasticity
<table>
<tr><th>Muscle</th><th>Recommended Dose and Number of Sites</th></tr>
<tr><td>Biceps Brachii</td><td>1.5 Units/kg to 3 Units/kg divided in 4 sites</td></tr>
<tr><td>Brachialis</td><td>1 Units/kg to 2 Units/kg divided in 2 sites</td></tr>
<tr><td>Brachioradialis</td><td>0.5 Units/kg to 1 Units/kg divided in 2 sites</td></tr>
<tr><td>Flexor Carpi Radialis</td><td>1 Units/kg to 2 Units/kg divided in 2 sites</td></tr>
<tr><td>Flexor Carpi Ulnaris</td><td>1 Units/kg to 2 Units/kg divided in 2 sites</td></tr>
<tr><td>Flexor Digitorum Profundus</td><td>0.5 Units/kg to 1 Units/kg divided in 2 sites</td></tr>
<tr><td>Flexor Digitorum Sublimis</td><td>0.5 Units/kg to 1 Units/kg divided in 2 sites</td></tr>
</table>

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.
Primary Axillary Hyperhidrosis: 50 Units per axilla
Blepharospasm: The initial recommended dose is 1.25 Units-2.5 Units into each of 3 sites per affected eye. The cumulative dose of Botox treatment for blepharospasm in a 30-day period should not exceed 200 Units.
Strabismus:
Initial Doses in Units
Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

Subsequent Doses for Residual or Recurrent Strabismus

It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two –fold compared to the previously administered dose.
Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
The maximum recommended dose as a single injection for any one muscle is 25 Units.

</td></tr>
<tr><td>Dysport</td><td>**Refer to the prescribing information (product label) for complete dosing information.
<u>Cervical Dystonia</u></td></tr>
</table>

Brand	Recommended Dosing
	• Initial dose is 500 Units given intramuscularly as a divided dose among the affected muscles in patients with or without a history of prior treatment with botulinum toxin. • Re-treatment every 12 to 16 weeks or longer, as necessary, based on return of clinical symptoms with doses administered between 250 and 1000 Units to optimize clinical benefit • Re-treatment should not occur in intervals of less than 12 weeks • Titrate in 250 Unit steps according to patient's response <u>Glabellar Lines</u> • Administer a total dose of 50 Units, divided in five equal aliquots of 10 Units each, intramuscularly to affected muscles to achieve clinical effect • Re-treatment should be administered no more frequently than every 3 months <u>Spasticity in Adults</u> • Select dose based on muscles affected, severity of spasticity, and treatment and adverse reaction history with botulinum toxins • Dosing for upper limb spasticity: between 500 Units and 1000 Units • Dosing for lower limb spasticity: up to 1500 Units • The maximum recommended total dose per treatment session (upper and lower limb combined) in adults is 1500 Units • Re-treatment, based on return of clinical symptoms, should not occur in intervals of less than 12 weeks <u>Spasticity in Pediatric Patients</u> • Select dose based on the affected muscle, severity of spasticity, and treatment and adverse reaction history with all botulinum toxins. • Recommended dosing for upper limb spasticity: 8 Units/kg to 16 Units/kg per limb. The maximum recommended total dose administered per treatment session must not exceed 16 Units/kg or 640 Units, whichever is lower. • Recommended dosing for lower limb spasticity: 10 Units/kg to 15 Units/kg per limb. Total dose per treatment session must not exceed 15 Units/kg for unilateral lower limb injections, 30 Units/kg for bilateral injections, or 1000 Units, whichever is lower. • The maximum recommended total dose per treatment session is 30 Units/kg or 1000 Units, whichever is lower. Retreatment, based on return of clinical symptoms, should not occur in intervals of less than 3 months. The safety and effectiveness of Dysport injected into proximal muscles of the lower limb for the treatment of spasticity in pediatric patients has not been established.
Xeomin	***Refer to the prescribing information (product label) for complete dosing information.* The recommended maximum cumulative dose for any indication should not exceed 400 Units in a treatment session. **Blepharospasm:** • In treatment-naïve patients, the recommended initial dose of Xeomin is 50 Units (25 Units per eye). • In patients previously treated with botulinum toxin A, their past dose, response to treatment, duration of effect, and adverse event history should be taken into consideration when determining the Xeomin dose. • The total dose of Xeomin should not exceed 100 Units per treatment session (50 Units per eye). **Cervical Dystonia:** • The recommended initial dose of Xeomin for cervical dystonia is 120 Units.

<table>
<tr><th>Brand</th><th>Recommended Dosing</th></tr>
<tr><td></td><td>

In a placebo-controlled trial utilizing initial Xeomin doses of 120 Units and 240 Units, no meaningful difference in effectiveness was demonstrated between the doses.
In previously treated patients, their past dose, response to treatment, duration of effect, and adverse event history should be taken into consideration when determining the Xeomin dose.
The frequency of Xeomin repeat treatments should be determined by clinical response, but should generally be no more frequent than every 12 weeks.

Chronic Sialorrhea:

Chronic Sialorrhea in Adults: The recommended total dose is 100 Units per treatment session consisting of 30 Units per parotid gland and 20 Units per submandibular gland, no sooner than every 16 weeks
Chronic Sialorrhea in Pediatric Patients: The recommended dose is based on body weight administered in a 3:2 dose ratio into the parotid and submandibular glands, respectively, no sooner than every 16 weeks; ultrasound guidance recommended

Glabellar Lines:

The recommended dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each.
The five injection sites are: two injections in each corrugator muscle and one injection in the procerus muscle.
Retreatment with Xeomin should be administered no more frequently than every three months.

Upper limb spasticity in Adult Patients:

The dosage, frequency, and number of injection sites should be tailored to the individual patient based on the size, number, and location of muscles to be treated, severity of spasticity, presence of local muscle weakness, patient’s response to previous treatment, and adverse event history with Xeomin.
The frequency of Xeomin treatments should be no sooner than every 12 weeks.
In patients not previously treated with botulinum toxins, initial dosing should begin at the low end of the recommended dosing range and titrated as clinically necessary.

Xeomin Dosing by Muscle for Treatment of Adult Upper Limb Spasticity
<table>
<tr><th>Clinical Pattern
Muscle</th><th>Units (Range)</th><th>Number of injection sites per muscle</th></tr>
<tr><td>Clenched Fist
Flexor digitorum superficialis
Flexor digitorum profundus</td><td>
25 Units-100 Units
25 Units-100 Units</td><td>
2
2</td></tr>
<tr><td>Flexed Wrist
Flexor carpi radialis
Flexor carpi ulnaris</td><td>
25 Units-100 Units
20 Units-100 Units</td><td>
1-2
1-2</td></tr>
<tr><td>Flexed Elbow
Brachioradialis
Biceps
Brachialis</td><td>
25 Units-100 Units
50 Units-200 Units
25 Units-100 Units</td><td>
1-3
1-4
1-2</td></tr>
<tr><td>Pronated Forearm
Pronator quadratus
Pronator teres</td><td>
10 Units-50 Units
25 Units-75 Units</td><td>
1
1-2</td></tr>
<tr><td>Thumb-in-Palm
Flexor pollicis longus
Adductor pollicis
Flexor pollicis brevis/
Opponens pollicis</td><td>
10 Units-50 Units
5 Units-30 Units
5 Units-30 Units</td><td>
1
1
1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Brand</th><th>Recommended Dosing</th></tr>
<tr><td></td><td>
Upper Limb Spasticity in Pediatric Patients, Excluding Spasticity Caused by Cerebral Palsy

The exact dosage, frequency, and number of injection sites should be tailored to the individual patient based on size, number and localization of involved muscles; the severity of spasticity; and the presence of local muscle weakness.
The maximum recommended dose is 8 Units/kg, divided among affected muscles, up to a maximum dose of 200 Units per single upper limb. If both upper limbs are treated, total Xeomin dosage should not exceed 16 Units/kg, up to a maximum of 400 Units.
The timing for repeat treatment should be determined based on the clinical need of the patient; the frequency of repeat treatments should be no sooner than every 12 weeks.

Xeomin Dosing by Muscle for Treatment of Pediatric Upper Limb Spasticity, Excluding Spasticity Caused by Cerebral Palsy
<table>
<tr><th rowspan="2">Clinical Pattern
Muscle</th><th colspan="2">Dosage</th><th rowspan="2">Number of injection sites per muscle</th></tr>
<tr><th>Range (Units/kg)</th><th>Maximum (Units)</th></tr>
<tr><td>Flexed Elbow
Brachioradialis
Biceps
Brachialis</td><td>
1-2
2-3
1-2</td><td>
50
75
50</td><td>
1-2
1-3
1-2</td></tr>
<tr><td>Flexed Wrist
Flexor carpi radialis
Flexor carpi ulnaris</td><td>
1
1</td><td>
25
25</td><td>
1
1</td></tr>
<tr><td>Pronated Forearm
Pronator quadratus
Pronator teres</td><td>
0.5
1-2</td><td>
12.5
50</td><td>
1
1-2</td></tr>
<tr><td>Clenched Fist
Flexor digitorum superficialis
Flexor digitorum profundus</td><td>
1
1</td><td>
25
25</td><td>
1
1</td></tr>
<tr><td>Thumb-in-Palm
Flexor pollicis longus
Adductor pollicis
Flexor pollicis brevis/ Opponens pollicis</td><td>
1
0.5
0.5</td><td>
25
12.5
12.5</td><td>
1
1
1</td></tr>
</table>
</td></tr>
</table>

Drug Availability

Brand Name	Drug Availability
Botox	Botox is supplied in single-use vials of 50 Units, 100 Units or 200 Unit vials for reconstitution. Botox Cosmetic is also supplied in 50 Units or 100 Unit vials for reconstitution.
Dysport	Dysport for injection is supplied as single-use 300 Unit or 500 Unit vials of lyophilized powder for reconstitution. The 500 Unit vial is packaged as 1 or 2 vials per box.
Xeomin	Xeomin is supplied in single-use vials of 50 Units, 100 Units and 200 Units of lyophilized powder for reconstitution.

General Background

Pharmacology

Botulinum toxins work in the peripheral and autonomic nervous systems by preventing the release of acetylcholine. This effect results in disrupted neurotransmission and muscle paralysis. Clostridium botulinum (C. botulinum), C. baratii, and C. butyricum all produce the neurotoxin, botulinum. The available formulations of botulinum therapy are derived from Clostridium botulinum. It specifically has been demonstrated to cleave

synaptic vesicle associated membrane protein (VAMP, i.e. synaptobrevin), which is a component of the protein complex responsible for docking and fusion of the synaptic vesicle to the pre-synaptic membrane, a necessary step to neurotransmitter release. There are seven antigenically different types of botulinum toxin: A, B, C, D, E, F, and G. Antitoxin to a specific botulinum toxin such as anti-A botulinum does not neutralize the effects of other types of toxins such as types B through G. Botulinum toxin doses are expressed in units of biologic activity, with one unit corresponding to the lethal dose for female Swiss-Webster mice. However, the different botulinum formulations are not interchangeable because assays measuring the lethal dose differ. Systemic concentrations of botulinum toxin following intradermal or intramuscular injection are not expected.

Professional Societies/Organizations

American Academy of Neurology (AAN)

The AAN has several practice guidelines providing recommendations for and against the use of botulinum neurotoxin and, in some conditions, have product specific recommendations. The AAN provides several levels of recommendations. Level A recommendations in favor of effectiveness means the intervention should be offered; level B or C indicates the intervention should be considered or may be considered, respectively; and level U means there is insufficient evidence to support or refute effectiveness. In addition, there are 2 levels of recommendations for ineffectiveness of an intervention (level A means the intervention should not be offered and level B means the intervention should not be considered).

The AAN provides recommendations for the use of botulinum neurotoxin for the following conditions:

- **Blepharospasm** (Botox and Xeomin, Level B; Dysport, Level C; Myobloc, Level U) (Simpson, 2016)
- **Cervical dystonia** (Dysport and Myobloc, Level A; Botox and Xeomin, Level B) (Simpson, 2016)
- **Detrusor sphincter dyssynergia** in spinal cord injury (botulinum therapy, Level B) (Naumann, 2008)
- **Drooling** (botulinum therapy, Level B) (Naumann, 2008)
- **Focal limb dystonia** (botulinum therapy, Level B) (Simpson, 2008)
- **Gustatory sweating** (botulinum therapy, Level C) (Naumann, 2008)
- **Hemifacial spasm** (Botox and Dysport are possibly equivalent, Level C) (Simpson, 2008)
- **Hyperhidrosis – axillary** (botulinum therapy, Level A) (Naumann, 2008)
- **Hyperhidrosis – palmer** (botulinum therapy, Level B) (Naumann, 2008)
- **Laryngeal dystonia** (botulinum therapy, Level B) (Simpson, 2008)
- **Motor tics** (botulinum therapy, Level C) (Simpson, 2008)
- **Neurogenic detrusor overactivity** (botulinum therapy, Level A) (Naumann, 2008)
- **Spasticity**
  - Upper limb spasticity in adults (Dysport, Xeomin, and Botox, Level A; Myobloc, Level B) (Simpson, 2016)
  - Lower limb spasticity in adults (Botox and Dysport, Level A; Xeomin and Myobloc, Level U) (Simpson, 2016)
  - AAN guidelines make no recommendations for using one specific botulinum toxin product over another in adults due to lack of comparative trials (Simpson, 2016)
  - Spasticity in children and adolescents with cerebral palsy (Delgado, 2010)
    - Botulinum toxin A for localized/segmental spasticity in the upper and lower extremities (Level A)
    - Botulinum toxin A to improve motor function (Level U)
    - Botulinum toxin B (Level U)
    - AAN guidelines make no recommendations for using one specific botulinum toxin product over another in children and adolescents (Delgado, 2010)
- **Tremor** (botulinum therapy for essential hand tremor in those who fail treatment with oral agents, Level B) (Simpson, 2008); (botulinum toxin for essential tremor, Level C) (Zesiewicz, 2011)
- **Chronic migraine headache** (Botox)
  The AAN notes that Botox is a treatment option to increase the number of headache-free days (Level A) and may be considered to reduce headache impact on health-related quality of life (Level B). (Silberstein, 2012)

American Headache Society (AHS) and American Academy of Neurology (AAN)

An updated concensus statement on integrating new migraine treatments into clinical practice for the preventive and acute treatment of migraine by the American Headache Society reaffirms previous migraine guidelines. (AHS, 2021) Patients with migraine should be considered for preventive treatment when attacks significantly interfere with patients' daily routines despite acute treatment; frequent attacks (4 or more monthly headache

days); contraindication to, failure, overuse, or adverse events with acute treatments; or patient preference. Before developing a preventive treatment plan, the appropriate use (e.g., drug type, route and timing of administration, frequency) of acute treatments should be initiated and coupled with education and lifestyle modifications. All patients with migraine should be offered a trial of acute treatment. Based on the level of evidence for efficacy and the American Academy of Neurology (AAN) scheme for classification of evidence, the following oral treatments have established efficacy and should be offered for migraine prevention: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate [not for women of childbearing potential without a reliable method of birth control]); beta-blockers (metoprolol, propranolol, timolol); frovatriptan (for short-term preventive treatment of menstrual migraine); and angiotensin receptor blockers (candesartan). The following treatments are probably effective and should be considered for migraine prevention: angiotensin converting enzyme inhibitors (lisinopril), antidepressants (amitriptyline, venlafaxine) and beta-blockers (atenolol, nadolol). (Silberstein, 2012; AHS, 2021)

AAN concludes that Botox is ineffective for episodic migraine (Level A) and tension-type headache (Level B). (Simpson, 2016) AAN notes there is insufficient data to support or refute the use of botulinum toxin type A for tardive syndromes (Level U). (Bhidayasiri, 2013)

American College of Gastroenterology (ACG)

- **Achalasia**

The ACG provides guidelines for the diagnosis and management of achalasia. The ACG makes a strong recommendation based on moderate quality evidence for botulinum toxin for individuals who are not candidates for pneumatic dilation or surgical myotomy. (Vaezi, 2013)

American Heart Association/American Stroke Association (AHA/ASA)

- **Adult Spasticity**

The AHA/ASA guidelines for stroke rehabilitation discuss use of botulinum toxin for post-stroke spasticity, but do not include product-specific recommendations. In patients with upper limb spasticity, botulinum toxin is recommended (Level A) to reduce spasticity, improve range of motion, and improve dressing, hygiene, and limb positioning. Botulinum neurotoxin is recommended (Level A) for lower limb spasticity that interferes with gait. Botulinum neurotoxin is the only pharmacologic treatment with a Class I, Level A recommendation for post-stroke spasticity according to the AHA/ASA guidelines. (Winstein, 2016)

American Urological Association/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (AUA/SUFU)

- **Overactive Bladder**

The AUA/SUFU recommends intradetrusor onabotulinumtoxinA injection as third-line therapy in select patients who have received adequate counseling and who have not responded to first and second line treatment. (Gormley 2014)

American Urological Association (AUA)

- **Interstitial Cystitis**

The AUA lists intradetrusor botulinum toxin A as a fourth-line treatment option (evidence strength C [low quality; low certainty]) if other treatments have not provided adequate symptom control and quality of life. In addition, the guideline notes that post-treatment intermittent self-catheterization may be necessary. The evidence provided supporting use includes a randomized controlled trial and multiple observational studies. First-line treatments are recommended for all patients and include education, self-care practices and behavioral modifications, and stress management practices. Second-line treatments include manual physical therapy techniques, multimodal pain management, oral pharmacotherapy (amitriptyline, cimetidine, hydroxyzine, pentosan polysulfate) and intravesical treatments (DMSO, heparin, lidocaine). Third-line treatments include cystoscopy under anesthesia with short-duration, low-pressure hydrodistension, and if Hunner's lesions are present, fulguration and/or injection of triamcinolone. (Hanno, 2014)

National Institute of Clinical Excellence (NICE)

- **Pediatric Spasticity**

NICE guidelines provide recommendations for young people with spasticity due to nonprogressive brain disorders, including Cerebral Palsy. Botulinum neurotoxin serotype A is recommended for children with focal

spasticity in the upper or lower limbs associated with pain, cosmetic concerns, inability to comply with nonpharmacologic treatments (physiotherapy, use of orthotic devices), or impaired motor function or ability to perform hygiene tasks. The NICE guidelines do not address specific botulinum neurotoxin products or provide recommendations for dosing or injection techniques. All patients should participate in an individualized physiotherapy program. Oral diazepam or oral baclofen are recommended for patients with spasticity associated with pain or functional disability. Intrathecal baclofen is recommended for spasticity not responding to other treatment options. Selective dorsal rhizotomy is recommended for ambulatory patients to improve walking. (Mugglestone, 2012)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative
No recommendations are available for Botox, Dysport, Myobloc or Xeomin.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for Botox, Dysport, Myobloc or Xeomin.

Clinical Efficacy
Botox

- **Chronic Migraine Headache**

FDA approval of Botox for chronic migraine headache (defined as 15 days or more per month with headache lasting 4 hours a day or longer) was based on the PREEMPT 1 and 2 trials. Adults (n = 679 for PREEMPT 1 and n = 705 for PREEMPT 2) with chronic migraine headache were randomized to either onabotulinumtoxinA (Botox) 155-195 units every 12 weeks or placebo. In both trials, the baseline mean headache days (per 28 days) was approximately 20 and the baseline mean cumulative hours of headache on headache days (per 28 days) was approximately 275-300 hours. (Aurora, 2010; Diener, 2010)

PREEMPT 1 was conducted in North American sites. There was no significant difference in the primary endpoint of change in headache episodes from baseline to week 24 compared to placebo (-5.2 Botox vs. -5.3 placebo; p = 0.344). There was a significant difference in change from baseline in frequency of headache days (-7.8 Botox vs. -6.4 placebo; p = 0.006) and change from baseline in total cumulative hours of headache on headache days (-107 Botox vs. -70 placebo; p = 0.003) for Botox compared to placebo. (Aurora, 2010)

PREEMPT 2 was conducted in North American and European sites. Unlike PREEMPT 1, the primary endpoint was mean change in headache days per 28 days from baseline to weeks 21-24 and was significantly in favor of Botox versus placebo (-9.0 Botox vs. -6.7 placebo; p < 0.001). The change from baseline in cumulative total headache hours on headache days was -132.4 hours with Botox compared to -90.0 hours with placebo (p < 0.001). (Diener, 2010)

Prophylactic treatment aims to reduce the frequency or severity of migraine headache attacks (Jackson, 2012), and may include pharmacologic and nonpharmacologic options. Although not specific to chronic migraine, guidelines for prevention of episodic migraine headache has been recommended by the American Academy of Neurology (AAN). Beta-blockers (e.g., metoprolol, propranolol) and anticonvulsant medications (e.g., divalproex, topirimate) received the highest quality evidence recommendations for pharmacologic treatment (Silberstein, 2013). Calcium channel blockers are listed as Level U for prophylaxis (insufficient data to support or refute). (Silberstein, 2013) In a recent Drug Safety Communication (2013), the Food and Drug Administration (FDA) advised that valproate sodium and related products, valproic acid and divalproex sodium, are contraindicated and should not be taken by pregnant women for the prevention of migraine headaches. With regard to women of childbearing age who are not pregnant, the FDA notes valproate should not be taken for any condition unless the drug is essential to the management of the woman's medical condition. All non-pregnant women of childbearing age taking valproate products should use effective birth control.

- **Frey Syndrome**

Botox A is used successfully for Frey syndrome, (i.e. gustatory sweating on the cheek), a condition that is fairly common after parotid gland surgery. Several studies involve the use of Botox compared to placebo and/or topical ointment applications. In all completed clinical studies, Botox injections prove to be to most efficacious and are recommended for use in this condition.

- **Intracranial Lesions or Cerebrovascular Accident-Induced Voiding Difficulty**

Chen and Kuo (2004) showed positive results with Botox A when comparing Botox A and no treatment in patients with urinary problems due to intracranial lesions or cerebrovascular accidents. Patients who received a urethral injection of Botox A demonstrated improved voiding pressure and increased maximum urine flow rates (+3.1 mL/sec) compared to baseline ($p<0.05$). No adverse effects or withdrawals were reported. (Chen, 2004)

- **Post-Stroke Upper Limb Spasticity**

Foley et al. (2012) reported results of a systematic review and meta-analysis of 16 randomized controlled trials involving 1000 patients with moderate to severe upper limb spasticity who were recovering from first or subsequent stroke. Study subjects received an injection of botulinumtoxin A to muscles in the shoulder, elbow, wrist, or fingers versus placebo or nonpharmacologic treatment. In pooled analysis, botulinum toxin (all formulations) was associated with a moderate treatment effect size ($p<.0001$). (Foley, 2012) Shaw et al. (2010) performed a multicenter open-label parallel-group RCT of 333 adult patients with upper limb spasticity at the shoulder, elbow, wrist or hand and reduced upper limb function due to stroke more than one month prior to the study. Patients received botulinum toxin type A injection(s) plus a four-week program of upper limb therapy versus an upper limb therapy program alone. Botulinumtoxin A resulted in improvement of at least one activity of daily living at one, three and 12 months ($p = 0.033$, $p = 0.027$, p value not reported, respectively) compared with therapy. Additionally, results with botulinumtoxin A were better than therapy for muscle tone/spasticity at one month; however, there was nonsuperiority of botulinum A compared with therapy a three and 12 months, and for improvement in arm function at one, three, or 12 months. (Shaw, 2010)

In an additional study Marciniak et al. (2012) reported results of a small randomized, placebo-controlled, double-blinded trial involving 21 adult patients with post-stroke shoulder spasticity. Patients were randomized to receive onabotulinumtoxinA (Botox A; 140-200 units), into the pectoralis major with or without injections to the teres major, or placebo (saline) injections. Neither onabotulinumtoxin A nor the placebo groups achieved statistically significant improvement on shoulder adductor tone at four weeks after injection. Significant improvement was noted for hygiene ($p = 0.016$) in the onabotulinumtoxin A group compared with placebo. A trend for improvement in dressing was also noted ($p = 0.061$). Data suggests that onabotulinumtoxin A may be an effective treatment for selected individuals with post-stroke upper limb spasticity. (Marciniak, 2012)

Botox and Dysport

- **Hirschsprung Disease**

Data supporting the use of botulinum therapy for obstructive symptoms in Hirschsprung's disease following surgery is limited to one prospective clinical trial of 18 children (Minkes, 2000) and several retrospective reviews (Basson, 2014; Han-Geurts, 2014; Hukkinen, 2014; Koivusalo, 2009; Patrus, 2011; Wester, 2015). Botulinum therapy (Botox and Dysport) was associated with improvement in obstructive symptoms and reductions in hospitalizations.

Sialorrhea

- **Botox**

In a double-blind, placebo-controlled study, the safety and efficacy of botulinum toxin type A [now referred to as OnabotulinumtoxinA] was evaluated for the treatment of sialorrhea in 32 patients with Parkinson's disease (PD). Patients were randomized to receive either 50 Units of Botox in each parotid gland or placebo. Individuals who received Botox demonstrated a reduction in drooling frequency and saliva production. No adverse events were recorded. Botulinum toxin type A injections appear safe and effective treatment for the management of Parkinson's Disease-related drooling. (Lagalla, 2006)

- **Xeomin**

The efficacy and safety of Xeomin [IncobotulinumtoxinA] for the treatment of chronic sialorrhea were evaluated in a double-blind, placebo-controlled clinical trial that enrolled a total of 184 patients with chronic sialorrhea resulting from Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury ,that was present for at least three months. Patients with a history of aspiration pneumonia, amyotrophic lateral sclerosis, salivary gland or duct malformation, and gastroesophageal reflux disease were excluded.
In the main phase, a fixed total dose of Xeomin (100 Units or 75 Units) or placebo was administered into the parotid and submandibular salivary glands in a 3:2 dose ratio. The co-primary efficacy variables were the change

in unstimulated Salivary Flow Rate (uSFR) and the change in Global Impression of Change Scale (GICS) at Week 4 post-injection. A total of 173 treated patients completed the main phase of the study. For both the uSFR and GICS, Xeomin 100 Units was significantly better than placebo. Xeomin 75 Units was not significantly better than placebo. (Xeomin PI, 2018)

- **Atropine**

The safety and efficacy of atropine for the treatment sialorrhea in Parkinson's Disease were evaluated in an open-label pilot study of sublingual atropine drops for the treatment of sialorrhea in 7 patients (6 with Parkinson's disease). Self-reported drooling severity showed a significant decline between baseline and 180 minutes and between baseline and 1 week. When measured objectively, saliva production also decreased significantly between baseline and the 1-week follow-up. (Hyson, 2002)

- **Glycopyrolate**

The safety and efficacy of glycopyrolate for the treatment of developmentally disabled children with sialorrhea were evaluated in a double-blind, placebo-controlled, crossover dose-ranging clinical trial. Thirty-nine children (34 with cerebral palsy) were enrolled in the trial. Participants were randomized to either a placebo arm or glycopyrolate arm, which employed two weight-based (less than or greater than 30 kg) dosage regimens. Twenty-seven participants completed the trial. Eight children dropped out due to adverse events, 1 of which was in the placebo arm. Glycopyrolate demonstrated greater efficacy (75 % decrease) compared to placebo (15% decrease) in the control of excessive sialorrhea in children with developmental disabilities. (Mier, 2000)
The safety and efficacy of glycopyrolate for the treatment sialorrhea in Parkinson's Disease were evaluated in a 4 week double-blind, placebo-controlled, crossover trial in 23 patients with Parkinson's Disease. Participants were randomized to receive either glycopyrolate (1 mg three times a day) or placebo. 39.1%) of individuals treated with glycopyrolate had a clinically relevant improvement of at least 30% vs 4.3%) in the placebo group. There were no significant differences in adverse events between glycopyrolate and placebo treatment. (Arbouw, 2010)

- **Scopolamine**

The safety and efficacy of transdermal scopolamine were evaluated for the treatment of sialorrhea in patients with cerebral palsy, epilepsy and autism in a double-blind, crossover, placebo-controlled clinical trial. Thirty individuals were randomized and treated with either scopolamine transdermal patches of placebo patches. Drooling decreases of 69-80% were observed in the scopolamine group, with the placebo group not demonstrating a significant decrease in drooling. (Mato, 2010)

Spasticity in Children

There are no experimental parallel trials comparing the efficacy of one botulinum neurotoxin product with another. One observational, single-center study of quadriplegic, nonambulant cerebral palsy patients with lower limb spasticity evaluated efficacy of abobotulinumtoxinA (n = 17) or onabotulinumtoxinA (n = 9). The choice of botulinum neurotoxin product was dependent on pharmacy stock and whether the patient had previously received one of the formulations. The mean Pediatric Profile Pain score at baseline was 42.2 points compared with 9.5 points at 3 months postinjection (mean reduction 32.7 points, $P < 0.001$). A subgroup analysis concluded that reduction in pain scores was not affected by the botulinum neurotoxin product administered. The mean reduction in pain score was 32 points (95% CI, 27.4 to 36.6) with abobotulinumtoxinA and 34.1 points with onabotulinumtoxinA (95% CI, 26.7 to 41.5). (Lundy, 2009)

Upper Limb Spasticity in Children

One meta-analysis of 6 trials compared efficacy of onabotulinumtoxinA plus occupational therapy (OT) with OT alone in children with cerebral palsy and impaired upper limb function (Sakzewski, 2014). Four additional randomized controlled trials compared efficacy of onabotulinumtoxinA with placebo, or physical therapy (PT)/OT in children with cerebral palsy and upper limb spasticity (Lidman, 2015, Speth 2005, Koman, 2013, Ferrari, 2014). OnabotulinumtoxinA (with or without PT/OT) was more effective than control based on Goal Attainment Scale (GAS) scores in the meta-analysis, and in achieving the primary outcome of 4 of the 5 additional randomized controlled trials. OnabotulinumtoxinA plus PT/OT and PT/OT alone were similarly effective in 1 randomized, controlled trial. One single-center retrospective study evaluated rimabotulinumtoxinB in children with upper or lower limb spasticity, and subjective treatment response was documented following 64% of injections (Brandenburg, 2013).

No randomized controlled trials have evaluated rimabotulinumtoxinB for treatment of upper limb spasticity in children, and no studies have evaluated efficacy of either abobotulinumtoxinA or incobotulinumtoxinA.

Lower Limb Spasticity Children

One meta-analysis of 15 trials evaluated efficacy of various botulinum neurotoxin serotype A products for treatment of calf spasticity in children. Results of the meta-analysis were equivocal. (Koog, 2010)

Koog et al conducted a meta-analysis of 15 randomized, controlled trials (N = 597) evaluating botulinum toxin serotype A for treatment of calf spasticity in children with CP. Two of the included trials were not published in English. Data were pooled based on control group (sham procedure or non-sham control) and timing of the efficacy assessment (< 2 months postintervention, 2 to 4 months postintervention, or > 4 months postintervention). Results were not reported for individual botulinum toxin products. Efficacy of botulinum serotype A for improving lower limb spasticity was not consistent. Botulinum neurotoxin serotype A was more effective than non-sham control (for example, standard care, Physical Therapy/Occupational Therapy) for improving modified Ashworth Scale (MAS) scores in the calf muscle at 2 to 4 months postinjection based on data from 5 trials with high heterogeneity (effect size: -1.72, 95% CI, -2.68 to -0.76, I^2 = 92%) and for improving passive ankle range of motion (ROM) at 2 to 4 months postinjection based on data from 4 trials with high heterogeneity (effect size: 1.002, 95% CI, 0.444 to 1.56, I^2 = 79%). Botulinum neurotoxin was not superior to control in most efficacy analyses comparing BoNT with sham procedures, or for improving gait speed and motor function regardless of the comparator group. No serious or long-term adverse events were reported following BoNT injections. (Koog, 2010)

Five randomized controlled trials other than those included in the meta-analysis evaluated onabotulinumtoxinA (with or without adjunct PT/OT) compared with control (sham injections, standard care, PT/OT, placebo) for lower limb spasticity in children. OnabotulinumtoxinA was superior to control in 3 studies using various outcomes to evaluate efficacy. OnabotulinumtoxinA was similar to control in 2 long-term trials. Three randomized controlled trials compared abobotulinumtoxinA with placebo in children with lower limb spasticity and assessed various efficacy outcomes. AbobotulinumtoxinA was more effective than placebo in 2 trials and was similar to placebo in 1 trial. One retrospective study evaluated subjective treatment response to rimabotulinumtoxinB in children with upper and lower limb spasticity as discussed above. (Copeland 2014, Tedroff 2010, Scholtes 2006, Barwood 2000, Graham 2008, Thorley 2012)

No studies have evaluated efficacy of incobotulinumtoxinA in children with lower limb spasticity.

Spasticity in Adults

There are no experimental parallel trials comparing one botulinum toxin with another for treatment of upper or lower limb spasticity in adults. OnabotulinumtoxinA efficacy was similar to abobotulinumtoxinA and incobotulinumtoxinA in 2 observational trials (Mohammadi 2010, Dressler 2009).

Upper Limb Spasticity in Adults

One meta-analysis of 7 trials evaluated the efficacy of botulinum toxin (abobotulinumtoxinA, onabotulinumtoxinA, or rimabotulinumtoxinB) (Elia, 2009) and 1 experimental parallel trial compared onabotulinumtoxinA with tizanidine or placebo (Simpson, 2009). Additional experimental parallel trials compared abobotulinumtoxinA (McCrory 2009, Shaw 2011, Rosales 2012, Lam 2012, Gracies 2015, Kaji 2010b), onabotulinumtoxinA (Kaji 2010, Simpson 2009), incobotulinumtoxinA (Kanovsky 2009, Elovic 2016), or rimabotulinumtoxinB (Gracies, 2014) with either placebo or standard care.

In the meta-analysis by Elia et al, abobotulinumtoxin A (350, 500, and 1,000 units) and onabotulinumtoxinA (75-360 units) were associated with statistically significant improvement in Ashworth scale (AS) score compared with placebo ($P \leq 0.02$). Improvement in Ashworth Scale score did not reach statistical significance with abobotulinumtoxinA 1,500 units or rimabotulinumtoxinB (10,000 units), but these analyses were based on small numbers of patients. AbobotulinumtoxinA significantly improved modified Ashworth scale (MAS) score compared with control in 5 trials ($P \leq 0.006$). AbobotulinumtoxinA was not significantly better than the control group in 2 trials that evaluated improved function of the upper limb or quality of life as the primary efficacy endpoints. OnabotulinumtoxinA was superior to tizanidine ($P = 0.001$) for improving modified Ashworth scale (MAS) scores in 1 trial. High-dose onabotulinumtoxinA was superior to placebo ($P < 0.001$) for improving MAS scores in 1 trial.

OnabotulinumtoxinA was not superior to placebo in 1 trial that evaluated improved active function and included patients with both upper and lower limb spasticity. IncobotulinumtoxinA was superior to placebo ($P < 0.001$) in 2 trials evaluating improvement AS scores as the primary outcome. RimabotulinumtoxinB was superior to placebo ($P = 0.028$) in 1 small, single-center trial evaluating elbow active range of motion.

Lower Limb Spasticity in Adults

Two trials compared abobotulinumtoxinA with placebo (Hyman 2000, Pittock 2003). AbobotulinumtoxinA 1,500 units was superior to placebo ($P = 0.02$) for improving passive range of motion in 1 trial. AbobotulinumtoxinA was not superior to placebo for increasing the distance walked in 2 minutes in the other trial. Three trials compared onabotulinumtoxinA with placebo (Ward, 2014, Dunne 2012, Kaji 2010). OnabotulinumtoxinA was superior to placebo for improving MAS (modified Ashworth scale) scores in 1 trial ($P = 0.006$), and was similar to placebo for improving AS (Ashworth scale) scores 1 trial. OnabotulinumtoxinA was not superior to placebo in 1 trial that evaluated improved active function and included patients with both upper and lower limb spasticity.

There are no published experimental parallel trials evaluating incobotulinumtoxinA or rimabotulinumtoxinB for treatment of lower limb spasticity in adults.

Off Label Uses

AHFS Drug Information 2019 Edition supports the following off-label uses:

- Botox - voiding dysfunction associated with BPH, uncomplicated chronic anal fissure, achalasia, spasmodic dysphonia (laryngeal dystonia), oromandibular dystonias and palmar hyperhidrosis
- Dysport – blepharospasm

AHFS Drug Information 2019 Edition does not support any off-label uses of Xeomin.

Anal Fissure

There is no consensus on dosage, specific site of administration, number of injections, or efficacy. The American Society of Colon and Rectal Surgeons (ASCRS) clinical practice guideline for the management of anal fissures state that results from several prospective studies suggest 20-60 Units of Botox provide healing rates between 18 to 71% within 9 weeks of treatment. And, botulinum toxin has demonstrated similar results to first line agents, topical calcium channel blockers, topical nifedipine and topical nitroglycerin. (Stewart, 2017)

Palmar Hyperhidrosis

The optimal Botox dosing for palmar hyperhidrosis is uncertain due to of a lack of studies. Some authors recommend a range from 50 to 100 Units per hand. The size of the hand can help to determine the optimal dose. Two to three Units should be used for each injection site. Muscle weakness in the hand is an issue and can be dose dependent. For this reason it is recommended to initiate treatment with 50 units per hand and reassess at 1 month. Injections have demonstrated activity for about 6 months and are thus usually repeated at 6 month intervals. (Weinberg, 2014)

Experimental, Investigational, Unproven Uses

Botulinum therapy is being studied for use in the following conditions. At this time, however, there are insufficient published data to demonstrate the safety and efficacy of the use of any specific agent in the botulinum therapy group for these indications.

- **Bruxism**

Limited published data is available evaluating the use of botulinum therapy in bruxism. Available data are from small, randomized controlled trials. One trial of 20 patients failed to demonstrate a significant benefit due to the small sample size. (Guarda-Nardini, 2008). Another trial of 12 patients (6 treated with botulinum therapy) demonstrated a reduction in the number of bruxism events. The authors concluded that their study supports the use of botulinum toxin injection as effective for nocturnal bruxism. (Lee, 2010)

- **Chronic Low Back Pain**

Emerging evidence suggests a role for botulinum injections in treating pain disorders. A Cochrane review screened references from studies, and consulted with content experts and Allergan. This included published and

unpublished randomized controlled trials without language restrictions. Three randomized trials (N =123 patients) were included in the review. Evidence from nineteen studies due to non-randomization, incomplete or unpublished data were excluded. Only one study included patients with chronic non-specific low back pain; the other two examined unique subpopulations. Only one of the three trials had a low risk of bias and demonstrated that botulinum injections reduced pain at three and eight weeks and improved function at eight weeks better than saline injections. The second trial showed that botulinum injections were better than injections of corticosteroid plus lidocaine or placebo in patients with sciatica attributed to piriformis syndrome. The third trial concluded that botulinum injections were better than traditional acupuncture in patients with third lumbar transverse process syndrome. There is low quality evidence that botulinum injections improved pain, function, or both better than saline injections and very low quality evidence that they were better than acupuncture or steroid injections. At this time there is insufficient evidence to demonstrate safety and effectiveness of botulinum therapy for the treatment of chronic low back pain. Further research is warranted and future trials should standardize patient populations, treatment protocols and comparison groups, enlist more participants and include long-term outcomes and clinical relevance of findings. (Waseem, 2011)

- **Gastroparesis**

Limited published data is available evaluating the use of botulinum therapy in gastroparesis. Available data are from small, randomized controlled trials. One trial of 23 patients failed to demonstrate a significant benefit compared to placebo. (Arts, 2007). Another randomized controlled trial of 32 patients failed to demonstrate superiority to placebo. (Friedenberg, 2008) The authors concluded that their study demonstrated that botulinum toxin is not superior to placebo in improving either symptoms or the rate of gastric emptying.

- **Headache**

More recent studies have focused on the use of botulinum toxin to reduce the frequency of headaches. The American Academy of Neurology (AAN) assessment identified three trials of botulinum toxin for episodic migraine, four studies of chronic daily headache, and four studies on chronic tension-type headaches. Most of the studies identified by the assessment stated that botulinum toxin A was used, and several further specified that they used Botox. The assessment concluded that botulinum toxin should not be considered for episodic migraine and chronic tension-type headache and that the evidence was insufficient for treatment of chronic daily headache. Of note the Indications and Usage section of the FDA prescribing label states “Important limitations: Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.” (Naumann, 2008)

Cervicogenic headache is a syndrome characterized by chronic hemicranial pain that is referred to the head from either bony structures or soft tissues of the neck. Diagnostic criteria have been established for cervicogenic headache, but its presenting characteristics occasionally may be difficult to distinguish from primary headache disorders such as migraine, tension-type headache, or hemicrania continua. A curative therapy for cervicogenic headache will not be developed until increased knowledge of the etiology and pathophysiology of the condition becomes available. Limited evidence suggests that therapy with botulinum toxin type A injected into pericranial and cervical muscles may be the most safe and efficacious approach, but further clinical and scientific study is needed.

There is no data evaluating the safety and efficacy of the combined use of calcitonin Gene-Related Peptide (CGRP) Inhibitors and onabotulinumtoxinA for the prevention of episodic or chronic migraine. The phase 2 trial of erenumab in chronic migraine did not permit concurrent use of botulinum therapy during the trial or at least 4 months prior. (Tepper, 2017)

- **Hemorrhoid Pain**

Thirty patients with thrombosed external hemorrhoids who refused surgical operation were randomized into two groups. Patients received an intrasphincteric injection of either 0.6 ml saline or 0.6 ml of a solution containing 30 units botulinum toxin. Anorectal manometry was performed before treatment and 5 days afterwards. After five days of treatment, the maximum resting pressure fell in both groups, but was significantly lower in the botulinum toxin group. Pain intensity was significantly reduced within 24 hours of botulinum toxin treatment compared with one week in the placebo group ($p = 0.019$). Although a single injection of botulinum toxin into the anal sphincter controlled pain associated with thrombosed external hemorrhoids in this study population larger, randomized

controlled trials are needed to demonstrate the safety and effectiveness of botulinum therapy for this indication. (Patti, 2008)

- **Lateral Epicondylitis**

Krogh et al (2013) conducted a systematic review and network meta-analysis of randomized controlled trials of effectiveness of injection therapies in lateral epicondylitis. Eight different injection therapies were analyzed, including 4 studies (N=133) evaluating botulinum toxin. Botulinum toxin was linked to paresis and weakness in the majority of patients in the extension of the wrist and the third and fourth fingers. The duration of this adverse event was described by 3 of the studies to have resolved by weeks 12 to 18. In regards to two previously published reviews which reported significant decreases in pain associated with botulinum treatment versus placebo, Krogh and colleagues state their evaluation does not demonstrate that botulinum toxin ameliorates maximum grip strength or reduces pain during maximum grip, and it is not known whether this therapy impacts function or pain-free grip strength. Despite botulinum toxin being slightly superior to placebo in this analysis, there was an increased risk of bias in these trials, as the authors point out these studies faced difficulty in blinding both the study subjects and the assessors, due to the paresis events. Consequently, results of these studies should be interpreted carefully.

- **Male Lower Urinary Tract Symptoms (LUTS)**

Gratzke et al (2015) authored guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS), including benign prostatic obstruction (BPO). The guidelines were derived from a review of 20 studies, using intraprostatic botulinum toxin injections for this condition, with a wide variety of evidence levels. Results reviewed from the largest placebo controlled study did not demonstrate a significant benefit in regards to the international prostate symptom score (IPSS), and other measures. For men with symptomatic moderate to severe LUTS, secondary to BPO or men who have urinary retention, the group views botulinum toxin therapy as an experimental therapy and should only be administered within the confines of a clinical study.

- **Myofascial Pain**

Soares et al. (2012) reported outcomes of a systematic review of four double-blinded randomized controlled trials with a total of 233 participants, comparing botulinum toxin A with placebo for the treatment of myofascial pain. Studies involving myofascial pain of the head and neck were excluded from this assessment. The authors noted that meta-analysis was not performed due to heterogeneity between studies. One study demonstrated a significant improvement rate of pain intensity scores ($p<0.00001$). No statistically significant difference was noted between botulinum toxin A versus placebo in the other three studies. The lack of methodological standardization (e.g., use of different pain scales, dosages and variations in the grouping strategies) limits the validity and reproducibility of the study conclusions. (Soares, 2012)

A systematic review by Ho et al. (2007) selected randomized controlled trials of trigger-point injection; use of the Oxford Pain Validity Scale was also a selection criterion. Five trials were included; one trial resulted in a significant effect, whereas the other four did not. The data were limited and the authors concluded that the evidence did not support the use of botulinum injections in trigger points for myofascial pain. There is insufficient evidence to support the effectiveness of botulinum toxin for the treatment of myofascial pain. (Ho, 2007)

- **Nausea and vomiting, post sleeve gastrectomy**

Limited published data is available evaluating the use of botulinum therapy in nausea and vomiting, post sleeve gastrectomy. Data is available from one randomized controlled trial. In the trial 115 individuals with morbid obesity and treated by laparoscopic sleeve gastrectomy were randomized 1:1, into two groups. Individuals in Group 1 received an intrapyloric botulinum toxin type-A injection and those in Group 2 received no injection. The primary outcome was number of patients developing a gastric leak. None of the individuals in the botulinum toxin group (N = 57) developed a gastric leak, while 4 individuals, who received no injection (N = 58) developed a gastric leak. Ten individuals in Group 1 and two patients in Group 2 developed refractory epigastric pain. Other adverse event rates were similar in each group. (Youssef, 2016)

- **Plantar Hyperhidrosis**

Limited published atea is available evaluating the use of botulinum toxin in the treatment of plantar hyperhidrosis. Data from 2 pilot studies (N = 12) demonstrated botulinum toxin as an effective and safe treatment for plantar hyperhidrosis. The authors concluded that botulinum toxin may be a useful agent in the treatment of plantar

hyperhidrosis, but clinical trials in larger patient sizes are necessary to evaluate the safety and effectiveness for this application. (Campanati, 2008; Vlahovic, 2008)

- **Spastic pelvic floor syndrome**

Limited published data is available evaluating the use of botulinum therapy in Spastic pelvic floor syndrome. Available data is from one small, randomized controlled trial. The trial in 60 women demonstrated a superiority in decreasing pelvic floor pressure, for the botulinum toxin group. The authors concluded that botulinum toxin type-A may be a useful agent in women with pelvic floor muscle spasm and chronic pelvic pain who do not respond to conservative physical therapy. (Abbott, 2006)

- **Sphincter of Oddi Dysfunction**

The protocol-based management of 25 patients with acalculous biliary pain and two gallbladder ejection fraction estimations less than 40% who had 100 units of botulinum toxin injected into their sphincter of Oddi (SO) musculature to relax the sphincter were audited (Murray, 2011). Patients whose pain was temporarily relieved after botulinum toxin injection were offered endoscopic biliary sphincterotomy, and patients who failed to experience benefit after botulinum toxin injection were assessed for laparoscopic cholecystectomy. Botulinum toxin was injected into the SO of 25 patients, with 11 experiencing temporary biliary pain relief. A total of 14 patients had a negative response to botulinum toxin treatment, with 10 of these patients progressing to laparoscopic cholecystectomy, which resulted in biliary pain relief in eight cases. (Murray, 2011) There is insufficient evidence to support the safety and effectiveness of botulinum toxin therapy for this indication.

- **Temporomandibular Joint (TMJ) Syndrome**

Twenty-one patients met specific criteria and were recruited from four Scandinavian clinics. Patients served as their own controls and were injected twice, once with Botox and once with saline, but in random order (crossover design). Investigators as well as subjects were blinded as to which substance was injected (double blinding). Pain intensity was reduced after both Botox and saline injections, although more so for Botox. However, the number of patients that experienced significant (defined as 30% decrease) pain reduction was about the same for both treatments. A strong placebo effect was noted. While there was a slightly better outcome for Botox than for saline, it was small and was not experienced by all patients. Further study is needed to determine safety and efficacy for the use of botulinum therapy in TMJ syndrome. (Ernberg, 2011)

- **Treatment of Tics**

Marras et al (2001) compared Botox A and placebo in patients with one or more motor tics due to Tourette syndrome or idiopathic tic disorder. Botox A treatment decreased the number of tics performed per minute by 39%, while patients treated with placebo experienced an increase in tic performance of 5.8% ($p<0.05$_. No differences between groups were noted in the Tourette Syndrome Global Score, Yale Global Tic Severity Scale, or Unified Tic Rating Scale. Appropriately 50% of patients experienced muscle weakness, and 10% experienced motor restlessness and the emergence of new tics. One patient withdrew from each group for unspecified reasons. (Marras, 2001) There is insufficient evidence to determine the safety and effectiveness of botulinum therapy for this indication.

- **Trigeminal Neuralgia**

Morra et al. synthesized evidence from published RCTs regarding safety and efficacy of botulinum toxin type A as a potential emerging choice of treatment for Trigeminal Neuralgia. A total of four RCTs (N =178 patients) were identified for final meta-analysis. The overall effect favored botulinum toxin type A versus placebo in terms of proportion of responders. Paroxysms frequency per day was significantly lower for the botulinum toxin group. The authors concluded that despite limited data, results suggest that botulinum toxin may be an effective and safe treatment option for patients with trigeminal neuralgia. Further larger and well-designed RCTs are warranted to verify these findings. (Morra, 2016)

- **Voiding Dysfunction Associated with Benign Prostatic Hyperplasia (BPH)**

In 2003, Maria and colleagues reported on 30 patients with BPH randomly assigned to receive either intraprostatic botulinum toxin A or saline injection. The mean peak urinary flow rate was significantly increased in the treatment group. (Maria, 2003) In 2006, Chuang reviewed trials testing the use of botulinum toxin in benign prostatic hyperplasia. With the exception of the previously cited trial by Maria and colleagues, all were small, open-label trials (n ranged from 8 to 52) that generally reported improvement in spontaneous voiding and

decreases in post-void residual volume compared to baseline. No additional trials were found to date. Given the prevalence of BPH, larger trials that compare the role of BPH with other medical and surgical therapies are warranted. (Chuang, 2006)

There is no data evaluating the safety and efficacy of botulinum toxin for the treatment cleft lip.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Neurologic Conditions

Covered when medically necessary when used to treat a covered neurologic condition:

CPT®* Codes	Description
31513	Laryngoscopy, indirect; with vocal cord injection
31570	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic
31571	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
31573	Laryngoscopy, flexible; with therapeutic injection(s) (eg, chemodenervation agent or corticosteroid, injected percutaneous, transoral, or via endoscope channel), unilateral
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous (eg, 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

HCPCS Codes	Description
J0585	Injection, OnabotulinumtoxinA, 1 unit
J0586	Injection, AbobotulinumtoxinA, 5 units
J0588	Injection, IncobotulinumtoxinA, 1 unit
S2340	Chemodenervation of abductor muscle(s) of vocal cord
S2341	Chemodenervation of adductor muscle(s) of vocal cord

Gastrointestinal Conditions

Covered when medically necessary when used to treat a covered gastrointestinal condition:

CPT®* Codes	Description
43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
46505	Chemodenervation of internal anal sphincter

HCPCS Codes	Description
J0585	Injection, OnabotulinumtoxinA, 1 unit
J0586	Injection, AbobotulinumtoxinA, 5 units

Exocrine Conditions

Covered when medically necessary when used to treat a covered exocrine condition:

CPT®* Codes	Description
64611	Chemodenervation of parotid and submandibular salivary glands, bilateral
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (eg, scalp, face, neck), per day
64999†	Unlisted procedure, nervous system

†Note: Covered when used to report chemodenervation of the hands for palmar hyperhidrosis.

HCPCS Codes	Description
J0585	Injection, OnabotulinumtoxinA, 1 unit
J0588	Injection, IncobotulinumtoxinA, 1 unit

Ophthalmologic Conditions

Covered when medically necessary when used to treat a covered ophthalmologic condition:

CPT®* Codes	Description
67345	Chemodenervation of extraocular muscle

HCPCS Codes	Description
J0585	Injection, OnabotulinumtoxinA, 1 unit

Urologic Conditions

Covered when medically necessary when used to treat a covered urologic condition:

CPT®* Codes	Description
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder

HCPCS Codes	Description
J0585	Injection, OnabotulinumtoxinA, 1 unit

***Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.**

References

1. 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. 2006 Oct; 108(4):915-23.
2. Allergan, Inc. Botox (onabotulinumtoxinA) [product information]. Irvine, CA: Allergan, Inc. March 2022.
3. American Headache Society. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021;61:7;1021-1039.
4. Arbouw ME, Movig KL, Koopmann M, et al. Glycopyrolate for sialorrhea in Parkinson disease: a randomized, double-blind, crossover trial. Neurology. 2010; 74(15):1203.
5. 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. 2007 Nov 1; 26(9):1251-8.
6. Aurora SK, Dodick DW, Turkel CC, et al on behalf of PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT I trial. Cephalalgia 2010; 30 (7): 793-803.
7. Barwood S, Baillieu C, Boyd R, et al. Analgesic effects of botulinum toxin A: a randomized, placebo-controlled clinical trial. Dev Med Child Neurol. 2000; 42(2):116-121.
8. Basson S, Charlesworth P, Healy C, et al. Botulinum toxin use in paediatric colorectal surgery. Pediatr Surg Int 2014; 30 (8): 833-8.
9. Bhidayasiri R, Fahn S, Weiner WJ, et al. Evidence-based guideline: Treatment of tardive syndromes: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013; 81 (5): 463-9.
10. Brandenburg JE, Krach LE, Gormley ME, Jr. Use of rimabotulinum toxin for focal hypertonicity management in children with cerebral palsy with nonresponse to onabotulinum toxin. Am J Phys Med Rehabil. 2013;92(10):898-904.
11. Campanati A, Bernardini ML, Gesuita R et al. Plantar focal idiopathic hyperhidrosis and botulinum toxin: a pilot study. Eur J Dermatol. 2007 Jan-Feb; 17(1):52-4.
12. Chen Y, Kuo H. Botulinum A toxin treatment of urethral sphincter pseudodyssynergia in patients with cerebrovascular accidents or intracranial lesions. Urol Int. 2004; 73(2):156-161; discussion 161-62.
13. Chuang YC, Chancellor MB. The application of botulinum toxin in the prostate. J Urol. 2006; 176(6 Pt 1):2375-82.
14. Copeland L, Edwards P, Thorley M, et al. Botulinum toxin A for nonambulatory children with cerebral palsy: a double blind randomized controlled trial. J Pediatr. 2014; 165(1):140-146 e144.
15. Delgado MR, Hirtz D, Aisen M, et al. Practice parameter: Pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2010; 74 (4): 336-43.
16. Diener HC, Dodick DW, Aurora SK, et al on behalf of the PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010; 30 (7): 804-814.
17. Dressler D. Routine use of Xeomin in patients previously treated with Botox: long term results. Eur J Neurol. 2009; 16 Suppl 2:2-5.
18. Dunne JW, Gracies JM, Hayes M, Zeman B, Singer BJ, Multicentre Study Group. A prospective, multicentre, randomized, double-blind, placebo-controlled trial of onabotulinumtoxinA to treat plantarflexor/invertor overactivity after stroke. Clin Rehabil. 2012; 26(9):787-797.
19. Elia AE, Filippini G, Calandrella D, Albanese A. Botulinum neurotoxins for post-stroke spasticity in adults: a systematic review. Mov Disord. 2009; 24(6):801-812.
20. Elovic EP, Munin MC, Kanovsky P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. Muscle Nerve. 2016; 53(3):415-421.
21. Ernberg M. et.al. Efficacy of botulinum toxin type A for treatment of persistent myofascial TMD pain: a randomized, controlled, double-blind multicenter study. Pain (2011), doi:10.1016/j.pain.2011.03.036.
22. Ferrari A, Maoret AR, Muzzini S, et al. A randomized trial of upper limb botulinum toxin versus placebo injection, combined with physiotherapy, in children with hemiplegia. Res Dev Disabil. 2014; 35(10):2505-2513.

23. Foley N, Pereira S, Salter K. Treatment With Botulinum Toxin Improves Upper-Extremity Function Post Stroke: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2012 Dec 19 ;(12)01224-5.
24. Food and Drug Administration. Drug safety communication: FDA Drug Safety Communication: Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children. 2013 May 6. Accessed at URL address: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM350748.pdf
25. Friedenberg FK, Palit A, Parkman HP, et al. Botulinum toxin A for the treatment of delayed gastric emptying. Am J Gastroenterol. 2008 Feb; 103(2):416-23.
26. Gormley E, Lightner D, Burgio K, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. 2014. Available at:http://www.auanet.org/common/pdf/education/clinical-guidance/Overactive-Bladder.pdf
27. Gracies JM, Brashear A, Jech R, et al; International AbobotulinumtoxinA Adult Upper Limb Spasticity Study Group. Safety and efficacy of abobotulinumtoxinA for hemiparesis in adults with upper limb spasticity after stroke or traumatic brain injury: a double-blind randomised controlled trial. Lancet Neurol. 2015; 14(10):992-1001.
28. Graham HK, Boyd R, Carlin JB, et al. Does botulinum toxin a combined with bracing prevent hip displacement in children with cerebral palsy and "hips at risk"? A randomized, controlled trial. J Bone Joint Surg Am. 2008; 90(1):23-33.
29. Gratzke C, Bachmann A, Descazeaud A et al. EAU Guidelines on the Assessment of Non-Neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. Eur Urol. 2015 Jun; 67(6):1099-109.
30. Guarda-Nardini L, Manfredini D, Salamone M, et al. Efficacy of botulinum toxin in treating myofascial pain in bruxers: a controlled placebo pilot study. Cranio 2008; 26 (2): 126-35.
31. 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 2014; 59 (5): 604-7.
32. Hanno PM, Burks DA, Clemens JQ, et al. Diagnosis and treatment of interstitial cystitis/bladder pain syndrome. September 2014. Available at: https://www.auanet.org/education/guidelines/ic-bladder-pain-syndrome.cfm.
33. Ho KY, Tan KH. Botulinum toxin A for myofascial trigger point injection: a qualitative systematic review. Eur J Pain 2007; 11(5):519-27.
34. Hukkinen M, Koivusala A, Rintala RJ, Pakarinen MP. Restorative proctocolectomy with J-pouch ileoanal anastomosis for total colonic aganglionosis among neonates and infants. J Pediatr Surg 2014; 49 (4): 570-4.
35. Hyman N, Barnes M, Bhakta B, et al. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: a prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry. 2000; 68(6):707-712.
36. Hyson HC, Johnson AM, Jog MS. Sublingual atropine for sialorrhea secondary to parkinsonism: a pilot study. Mov Disord. 2002; 17(6):1318.
37. International Headache Society. ICHD-II. ©2013 International Headache Society. Accessed Oct 30, 2013. Available at URL address: http://www.ihs-headache.org/frame_non_members.asp
38. Ipsen Biopharmaceuticals, Inc. Dysport for injection (abobotulinumtoxinA) [product information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc. November 2018.
39. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis. JAMA. 2012 Apr 25; 307(26):1736-45.
40. Kaji R, Osako Y, Suyama K, et al; GSK1358820 Spasticity Study Group. Botulinum toxin type A in post-stroke upper limb spasticity. Curr Med Res Opin. 2010;26(8):1983-1992.
41. Kaji R, Osako Y, Suyama K, et al; GSK1358820 Spasticity Study Group. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. J Neurol. 2010b;257(8):1330-1337.
42. Kanovsky P, Slawek J, Denes Z, et al. Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity. Clin Neuropharmacol. 2009; 32(5):259-265.
43. Koman LA, Smith BP, Williams R, et al. Upper extremity spasticity in children with cerebral palsy: a randomized, double-blind, placebo-controlled study of the short-term outcomes of treatment with botulinum A toxin. J Hand Surg Am. 2013; 38(3):435-446 e431.
44. Koog YH, Min BI. Effects of botulinum toxin A on calf muscles in children with cerebral palsy: a systematic review. Clin Rehabil. 2010; 24(8):685-700.

45. Krogh T, Bartels E, Ellingsen T. Comparative Effectiveness of Injection Therapies in Lateral Epicondylitis: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. Am J Sports Med. 2013 Jun; 41(6):1435-46.
46. Lagalla G, Millevolte M, Capecci M, et al. Botulinum toxin type A for drooling in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord 2006; 21:704–707.
47. Lam K, Lau KK, So KK, et al. Can botulinum toxin decrease carer burden in long term care residents with upper limb spasticity? A randomized controlled study. J Am Med Dir Assoc. 2012; 13(5):477-484.
48. Lee SJ, McCall WD, Kim YK, et al. Effect of botulinum toxin injection on nocturnal brusism: a randomized controlled trial. Am J Phys Med Rehabil 2010; 89 (1): 16-23.
49. Lidman G, Nachemson A, Peny-Dahlstrand M, Himmelmann K. Botulinum toxin A injections and occupational therapy in children with unilateral spastic cerebral palsy: a randomized controlled trial. Dev Med Child Neurol. 2015; 57(8):754-761.
50. Lundy CT, Doherty GM, Fairhurst CB. Botulinum toxin type A injections can be an effective treatment for pain in children with hip spasms and cerebral palsy. Dev Med Child Neurol. 2009;51(9):705-710.
51. Marciniak C, Harvey R, Gagnon C, et al. Does botulinum toxin type A decrease pain and lessen disability in hemiplegic survivors of stroke with shoulder pain and spasticity?: a randomized, double-blind, placebo-controlled trial. Am J Phys Med Rehabil. 2012 Dec; 91(12):1007-19.
52. Maria G, Brisinda G, Civello I, et al. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. Urology 2003; 62(2):259-65.
53. Marras C, Andrews D, Sime E, et al. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology. Mar 13 2001; 56(5):605-610.
54. Mato A, Limeres J, Tomás I, et al. Management of drooling in disabled patients with scopolamine patches. Br J Clin Pharmacol. 2010 Jun; 69(6):684-8.
55. McEvoy GK, ed. 2019. AHFS Drug Information® - 60th Ed. Bethesda, MD. American Society of Health-System Pharmacists.
56. McCrory P, Turner-Stokes L, Baguley IJ, et al. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomized placebo-controlled study of the effects on quality of life and other person-centered outcomes. J Rehabil Med. 2009; 41(7):536-544.
57. Merz Pharmaceuticals, LLC and Merz North American, Inc. Xeomin (incobotulinumtoxinA) [product information]. Greensboro, NC and Franksville, WI: Merz Pharmaceuticals, LLC and Merz North American, Inc. April 2021.
58. Mier RJ, Bachrach SJ, Lakin RC, Barker T, Childs J, Moran M. Treatment of sialorrhea with glycopyrolate: A double-blind, dose-ranging study. Arch Pediatr Adolesc Med. Dec 2000; 154(12):1214-1218.
59. Minkes RK, Langer JC. A prospective study of botulinum toxin for internal anal sphincter hypertonicity in children with Hirschsprung's disease. J Pediatr Surg 2000; 35 (12): 1733-6.
60. Mohammadi B, Balouch SA, Dengler R, Kollewe K. Long-term treatment of spasticity with botulinum toxin type A: an analysis of 1221 treatments in 137 patients. Neurol Res. 2010; 32(3):309-313.
61. 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. 2016 Dec; 17(1):63.
62. Mugglestone MA, Eunson P, Murphy MS, Guideline Development Group. Spasticity in children and young people with non-progressive brain disorders: summary of NICE guidance. BMJ. 2012;345:e4845
63. Murray, et.al. Botulinum toxin-induced relaxation of the sphincter of Oddi may select patients with acalculous biliary pain who will benefit from cholecystectomy. Surg Endosc. 2011 Mar; 25(3):813-6. Epub 2010 Jul 28.
64. National Institute of Neurological Disorders and Stroke, in cooperation with the American Academy of Neurology, American Headache Society, and National headache Foundation. 21st century prevention and management of migraine headaches. Clinical Courier. Sep 2001. Accessed April 2013. Available at URL address: http://www.ninds.nih.gov/doctors/OP129D_Clinical_Courier_fa.pdf
65. Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008; 70; 1707-1714.
66. Ondo W, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology. Jan 13 2004; 62(1):37-40.

67. Patrus B, Nasr A, Langer JC, Gerstle JT. Intrasphincteric botulinum toxin decreases the rate of hospitalization for postoperative obstructive symptoms in children with Hirschsprung disease. J Pediatr Surg 2011; 46 (1): 184-7.
68. Patti R, et.al. Randomized clinical trial of botulinum toxin injection for pain relief in patients with thrombosed external haemorrhoids. Br J Surg. 2008 Nov; 95(11):1339-43.
69. Pittock SJ, Moore AP, Hardiman O, et al. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis. 2003; 15(4):289-300.
70. Rosales RL, Kong KH, Goh KJ, et al. Botulinum toxin injection for hypertonicity of the upper extremity within 12 weeks after stroke: a randomized controlled trial. Neurorehabil Neural Repair. 2012; 26(7):812-821.
71. Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta-analysis. Pediatrics. 2014; 133(1):e175-204.
72. Scholtes VA, Dallmeijer AJ, Knol DL, et al. The combined effect of lower-limb multilevel botulinum toxin type a and comprehensive rehabilitation on mobility in children with cerebral palsy: a randomized clinical trial. Arch Phys Med Rehabil. 2006; 87(12):1551-1558.
73. Shaw L, Rodgers H, Price C et al; BoTULS investigators. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. Health Technol Assess. 2010 May; 14(26):1-113, iii-iv.
74. Shaw LC, Price CI, van Wijck FM, et al; BoTULS Investigators. Botulinum Toxin for the Upper Limb after Stroke (BoTULS) Trial: effect on impairment, activity limitation, and pain. Stroke. 2011;42(5):1371-1379.
75. Silberstein S, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78 (17): 1337-45. Erratum: Feb 2013; 80(9): 871.
76. Simpson DM, Blitzer A, Brashear A, et al. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008; 70 (19): 1699-1706.
77. Simpson DM, Gracies JM, Yablon SA, Barbano R, Brashear A, BoNT/TZD Study Team. Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatry. 2009; 80(4):380-385.
78. Simpson DM, Hallett, M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016; 86: 1818-26.
79. Soares A, Andriolo R, Atallah A, et al. Botulinum toxin for myofascial pain syndromes in adults. Cochrane Database Syst Rev. 2012 Apr 18; 4:CD007533.
80. Solstice Neurosciences, Inc. Myobloc (rimabotulinumtoxinB) injection [product information]. South San Francisco, CA: Solstice Neurosciences, Inc. August 2019.
81. Speth LA, Leffers P, Janssen-Potten YJ, Vles JS. Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy. Dev Med Child Neurol. 2005; 47(7):468-473.
82. Stewart DB Sr1, Gaertner W, Glasgow S, et al. Clinical Practice Guideline for the Management of Anal Fissures. Dis Colon Rectum. 2017 Jan; 60(1):7-14.
83. Tedroff K, Lowing K, Haglund-Akerlind Y, Gutierrez-Farewik E, Forssberg H. Botulinum toxin A treatment in toddlers with cerebral palsy. Acta Paediatr. 2010; 99(8):1156-1162.
84. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017; 16: 425-34.
85. Thorley M, Donaghey S, Edwards P, et al. Evaluation of the effects of botulinum toxin A injections when used to improve ease of care and comfort in children with cerebral palsy whom are non-ambulant: a double blind randomized controlled trial. BMC Pediatr. 2012;12:120.
86. Vaezi M, Pandolfino J, Vela M. ACG Clinical Guideline: Diagnosis and management of achalasia. Am J Gastroenterol 2013; doi: 10.1038/ajg.2013.196.
87. Vlahovic TC, Dunn SP, Blau JC et al. Injectable botulinum toxin as a treatment for plantar hyperhidrosis: a case study. J Am Podiatr Med Assoc. 2008 Mar-Apr; 98(2):156-9.
88. Ward AB, Wissel J, Borg J, et al; BEST Study Group. Functional goal achievement in post-stroke spasticity patients: the BOTOX Economic Spasticity Trial (BEST). J Rehabil Med. 2014; 46(6):504-513.

89. Waseem Z, Boulias C, Gordon A, et al. Botulinum toxin injections for low back pain and sciatica. Cochrane Database of Systematic Reviews. 2011, Issue 1. Art. No, CD008257. DOI: 10.1002/14651858. CD008257.pub2
90. Weinberg T, Solish N, Murray C. Botulinum neurotoxin treatment of palmar and plantar hyperhidrosis. Dermatol Clin. 2014 Oct; 32(4):505-15.
91. Wester T, Granström AL. Botulinum toxin is efficient to treat obstructive symptoms in children with Hirschsprung disease. Pediatr Surg Int 2015; 31 (3): 255-9.
92. Winstein CJ, Stein J, Arena R, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47(6):e98-e169
93. Youssef T, Abdalla E, El-Alfy K, et al. Impact of Botulinum Neurotoxin Pyloric Injection During Laparoscopic Sleeve Gastrectomy on Postoperative Gastric Leak: a Clinical Randomized Study. Obes Surg. 2016 Mar; 26(3):494-504.
94. 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 2011; 77 (19): 1752-5.

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