UnitedHealthcare

DRUG POLICY

BOTULINUM TOXINS A AND B

Policy Number: 2014D0017N
Effective Date: 9/1/2014

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Related Medical or Drug Policies:
Temporomandibular Joint Disorders

Occipital Neuralgia and Headache Treatment

Related Coverage Determination Guidelines:
None

INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

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

COVERAGE RATIONALE

This policy refers to the following drug products:

Botulinum toxin type A
- abobotulinumtoxinA (Dysport™)
- incobotulinumtoxinA (Xeomin®)
- onabotulinumtoxinA (Botox®)

Botulinum toxin type B
- rimabotulinumtoxinB (Myobloc®)

The following information pertains to medical necessity review:

A. General Requirements (applicable to **all** medical necessity requests)**:**
1) For **initial therapy**, **both** of the following:

a. Diagnosis
AND
b. Medical records documenting **both** of the following:
1. History and physical examination documenting the severity of the condition
AND
2. Laboratory results or diagnostic evidence supporting the indication for which botulinum toxin is requested

2) For **continuation of therapy, both** of the following:
a. Documentation of positive clinical response to botulinum toxin therapy
AND
b. Statement of expected frequency and duration of proposed botulinum toxin treatment

3) Frequency of botulinum toxin administration, regardless of diagnosis, does not exceed every 12 weeks

B. Diagnosis-Specific Requirements
The information below indicates additional requirements for those indications having specific medical necessity criteria in the list of proven indications.

AbobotulinumtoxinA (Dysport, botulinum toxin type A) is **proven** in the treatment of the following conditions:

1) Achalasia[31,38-41,44]

Additional information to support medical necessity review where applicable:
AbobotulinumtoxinA is **medically necessary** for the treatment of achalasia when **both** of the following criteria are met:
A. Diagnosis of achalasia
AND
B. History of failure, contraindication, or intolerance to **one** of the following: *Refer to Benefit Considerations for specific state guidance*.
1. Long-acting nitrate
2. Calcium channel blocker

2) Anal fissures, chronic[25-30,36-7,303]

Additional information to support medical necessity review where applicable:
AbobotulinumtoxinA is **medically necessary** for the treatment of chronic anal fissures when **all** of the following criteria are met:
A. Diagnosis of chronic anal fissure
AND
B. At least 2 months of symptoms including **one** of the following:
1. Nocturnal pain and bleeding
2. Postdefecation pain
AND
C. History of failure, contraindication, or intolerance to **two** of the following conventional therapies: *Refer to Benefit Considerations for specific state guidance*.
1. Topical nitrate
2. Oral calcium channel blocker (e.g., diltiazem, nifedipine)
3. Topical calcium channel blocker (e.g., diltiazem, nifedipine)

3) Cervical dystonia (also known as spasmodic torticollis)[81,147,303,305-6]

Additional information to support medical necessity review where applicable:
AbobotulinumtoxinA is **medically necessary** for the treatment of cervical dystonia when **both** of the following criteria are met:

A. Diagnosis of cervical dystonia
AND
B. Symptoms including **both** of the following:
1. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

4) Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease[52,63,110-1,117-21,138,141,143-4,146,252-3,255,260,278-80,303]

Additional information to support medical necessity review where applicable:
AbobotulinumtoxinA is **medically necessary** when **both** of the following criteria are met:
A. **One** of the following:
1. Diagnosis of detrusor overactivity
2. Diagnosis of detrusor-sphinctor dyssynergia due to spinal cord injury or disease
AND
B. History of failure, contraindication, or intolerance to **two** anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine) *Refer to Benefit Considerations for specific state guidance*.

5) Hand dystonia (writer's, musician's or typist's cramp)[147,303,305]
6) Hand tremor[12-3,43,147,166,303]
7) Hemifacial spasm (seventh cranial nerve disorders)[84-7,104-8,147,165,303]
8) Hyperhidrosis[1,138,303] including gustatory sweating (Frey's Syndrome)[45-8,76,136-8,192]
9) Oromandibular dystonia[4-7,11,126]
10) Piriformis syndrome[99-100,244]
11) Sialorrhea[54,66-8,101,112-5,138,246,268,303]
12) Spasmodic dysphonia (laryngeal dystonia)[4,8-10,147]
13) Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or tumor of the brain or spinal cord[1,21-4,49,92-3,196-9,303]
14) Strabismus and blepharospasm associated with dystonia[1,147,303]
15) Tongue dystonia[4-7,11,126]
16) Torsion dystonia[3,4,7]
17) Voice tremor[9,16-17,167]

IncobotulinumtoxinA (Xeomin, botulinum toxin type A) is **proven** in the treatment of the following conditions:
1) Blepharospasm associated with dystonia[288,297]
2) Cervical dystonia (spasmodic torticollis)[288,297,305-6]

Additional information to support medical necessity review where applicable:
IncobotulinumtoxinA is **medically necessary** for the treatment of cervical dystonia (spasmodic torticollis) when **both** of the following criteria are met:
A. Diagnosis of cervical dystonia
AND
B. Symptoms including **both** of the following:
1. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

3) Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or

tumor of the brain or spinal cord[282-3,297]

OnabotulinumtoxinA (Botox, botulinum toxin type A), is **proven** in the treatment of the following conditions:

1) Achalasia[31,38-41,44,302]

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is **medically necessary** for the treatment of achalasia when **both** of the following criteria are met:

A. Diagnosis of achalasia
AND
B. History of failure, contraindication, or intolerance to **one** of the following: *Refer to Benefit Considerations for specific state guidance*.
   1. Long-acting nitrate
   2. Calcium channel blocker

2) Anal fissures, chronic[25-30,36-7,302]

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is **medically necessary** for the treatment of chronic anal fissures when **both** of the following criteria are met:

A. Diagnosis of chronic anal fissure
AND
B. At least 2 months of symptoms including **one** of the following:
   1. Nocturnal pain and bleeding
   2. Postdefecation pain
AND
C. History of failure, contraindication, or intolerance to **two** of the following conventional therapies: *Refer to Benefit Considerations for specific state guidance*.
   1. Topical nitrates
   2. Oral calcium channel blockers (e.g., diltiazem, nifedipine)
   3. Topical calcium channel blockers (e.g., diltiazem, nifedipine)

3) Cervical dystonia (also known as spasmodic torticollis)[1,81,302,305-6]

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is **medically necessary** for the treatment of cervical dystonia when **both** of the following criteria are met:

A. Diagnosis of cervical dystonia
AND
B. Symptoms including **both** of the following:
   1. Sustained head tilt or abnormal posturing resulting in pain and/or functional impairment
   2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

4) Detrusor overactivity (also known as detrusor hyperreflexia) or detrusor-sphincter dyssynergia due to spinal cord injury or disease[52,63,110-1,117-21,138,141,143-4,146,252-3,255,260,278-80,303]

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is **medically necessary** when **both** of the following criteria are met:

A. **One** of the following:
   1. Diagnosis of detrusor overactivity

2. Diagnosis of detrusor-sphinctor dyssynergia due to spinal cord injury or disease
AND

B. History of failure, contraindication, or intolerance to **two** anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine) *Refer to Benefit Considerations for specific state guidance*.

5) Hand dystonia (writer's, musician's or typist's cramp)[147,302,305]
6) Hand tremor[12-3,43,147,166,302]
7) Hemifacial spasm (seventh cranial nerve disorders)[84-7,104-8,147,165,302]
8) Hyperhidrosis[1,138,302] including gustatory sweating (Frey's Syndrome)[45-8,76,136-8,192]
9) Migraine headache, chronic[1,287,289,300,302] defined by **both** of the following:
   A. Greater than or equal to 15 headache days per month, of which at least 50% are migraine or probable migraine
   B. Headaches last 4 hours per day or longer

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is **medically necessary** for the prophylaxis of chronic migraine when **all** of the following criteria are met:

A. Diagnosis of chronic migraine, defined by **both** of the following:
   1. Greater than or equal to 15 headache days per month, of which at least 50% are migraine or probable migraine
   2. Headaches last 4 hours per day or longer
   AND
B. History of failure (after a trial of at least two months), contraindication, or intolerance to prophylactic therapy with one agent from **two** of the following therapeutic classes: *Refer to Benefit Considerations for specific state guidance*.
   1. Antiepileptic drug (e.g., divalproex sodium, sodium valproate, topiramate)
   2. Beta blocker (e.g., metoprolol, propranolol, timolol)
   3. Antidepressant (e.g., amitriptyline, venlafaxine)
   4. ACE inhibitor (e.g., lisinopril)
   5. Angiotensin receptor blocker (e.g., candesartan)
   6. Alpha agonist (e.g., clonidine, guanfacine)
   7. Antihistamine (e.g., cyproheptadine)
   AND
C. OnabotulinumtoxinA dose does not exceed 155 units administered intramuscularly divided over 31 injection sites every 12 weeks

10) Oromandibular dystonia[4-7,11,126]
11) Overactive bladder[1,302]

Additional information to support medical necessity review where applicable:
OnabotulinumtoxinA is **medically necessary** for the treatment of overactive bladder when **all** of the following criteria are met:

A. Diagnosis of overactive bladder
   AND
B. **One** of the following symptoms:
   1. Urge urinary incontinence
   2. Urgency
   3. Frequency
   AND
C. History of failure, contraindication, or intolerance to **two** anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine) *Refer to Benefit Considerations for specific state guidance*.
   AND

D. OnabotulinumtoxinA dose does not exceed 100 units divided over 20 injection sites every 12 weeks

12) Piriformis syndrome[99-100,244]
13) Sialorrhea[54,66-8,101,112-5,138,246,268,302]
14) Spasmodic dysphonia (laryngeal dystonia)[4,8-10,147,302]
15) Spasticity associated with cerebral palsy; multiple sclerosis; stroke; or other injury, disease, or tumor of the brain or spinal cord[1,21-4,49,92-3,196-9,302]
16) Strabismus and blepharospasm associated with dystonia[1,147,302]
17) Tongue dystonia[4-7,11,126,302]
18) Torsion dystonia[3,4,7,302]
19) Voice tremor[9,16-17,167]

RimabotulinumtoxinB (Myobloc, botulinum toxin type B) is proven in the treatment of the following conditions:

1) Cervical dystonia (also known as spasmodic torticollis)[2,305-6]

Additional information to support medical necessity review where applicable:
RimabotulinumtoxinB is **medically necessary** for the treatment of cervical dystonia when **both** of the following criteria are met:

A. Diagnosis of cervical dystonia
AND
B. Symptoms including **both** of the following:
1. Sustained head tilt or abnormal posturing ~~with limited range of motion~~ resulting in pain and/or functional impairment
2. Recurrent involuntary contraction of one or more muscles of the neck (e.g., sternocleidomastoid, splenius, trapezius, posterior cervical)

2) Detrusor overactivity (also known as detrusor hyperreflexia)[138,142,146]

Additional information to support medical necessity review where applicable:
RimabotulinumtoxinB is **medically necessary** when **both** of the following criteria are met:

A. Diagnosis of neurogenic detrusor overactivity
AND
B. History of failure, contraindication, or intolerance to **two** anticholinergic medications (e.g., oxybutynin, trospium, darifenacin, tolterodine) *Refer to Benefit Considerations for specific state guidance*.

3) Sialorrhea[116,138,267-9]

AbobotulinumtoxinA (Dysport), **incobotulinumtoxinA** (Xeomin), and **rimabotulinumtoxinB** (Myobloc) are **unproven** and not medically necessary for the treatment of chronic migraine headache.[34-5,131-2,138,168-9,170-1,108-7,281,296,303]

Botulinum toxin types A and B are **unproven** and not medically necessary for the treatment of the following conditions:

1) Acquired nystagmus[18-20,172-3]
2) Anismus (pelvic floor dyssynergia)[51,78,139,140]
3) Benign prostatic hyperplasia[109,130,146,285,302,303]
4) Brachial plexus palsy[69,70,237-8,302,303]
5) Chronic daily headache[133-135, 138,179,188,302,303]

6) Chronic low back pain[60,138,302]
7) Chronic prostatic pain[53,146]
8) Cricopharyngeal dysphagia[42,64-5,148-64]
9) Epiphora following salivary gland transplantation[77]
10) Esophageal spasm[74,190-1]
11) Gastroparesis (including diabetic gastroparesis)[89,90,98,145,270-7,~~290~~,302]
12) Gustatory epiphora (Crocodile tears)[48,77,193-5]
13) Head tremor[14-15]
14) Lateral epicondylitis (tennis elbow)[95,248-51]
15) Lichen simplex[94]
16) Lower urinary tract (voiding) dysfunction[71,88,122-3,146]
17) Motor tics[62,189]
18) Myofascial pain syndrome[59,75,96,226-36,290,303]
19) Nasal hypersecretion[83,247,284]
20) Pain and/or wound healing after hemorrhoidectomy[125,265-6]
21) Pancreas divisum[72]
22) Pelvic floor spasticity (and associated pain conditions)[146,291]
23) Postparotidectomy sialoceles[56]
24) Post-thoracotomy pseudoangina[75]
25) Proctalgia fugax[82,146,292]
26) Severe bruxism[57,80,205-12]
27) Severe paradoxical vocal cord movement[55,204]
28) Sphincter of Oddi dysfunction[50,102,200-3]
29) Stiff-person syndrome[97,254]
30) Temporomandibular disorders[58,213-25,243]
31) Tension headache[32-33,61,103,127-9,138,174-8,299]
32) Thyroid associated ophthalmopathy[73,239-42]
33) Tourette's syndrome[124,189,261-4]
34) Traumatic sixth nerve palsy[91,256-9]
35) Trigeminal neuralgia[293-295]
36) Trismus and stridor in amyotrophic lateral sclerosis[79,245]

Centers for Medicare and Medicaid Services (CMS):
National Coverage Determinations (NCDs) do not exist for botulinum toxins at this time. Local Coverage Determinations (LCDs) exist for the following botulinum toxin products: Botox (onabotulinumtoxinA), Myobloc (rimabotulinumtoxinB), Dysport (abobotulinumtoxinA) and Xeomin (incobotulinumtoxinA). Refer to the LCDs for Botulinum Toxins, Botulinum Toxin Type A & Type B, Botulinum Toxin Types A and B, Botulinum Toxin Types A and B Policy, Drugs and Biologicals: Botulinum Toxins and Chemodenervation.

Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

(Accessed May 16, 2014)

BENEFIT CONSIDERATIONS

Botulinum toxin type A and B are cosmetic when used to improve appearance, or in the absence of physiological functional impairment that would be improved by their use. Most UnitedHealthcare Certificates of Coverage (COCs) and Summary Plan Descriptions (SPDs) exclude benefit coverage for cosmetic services. In addition, most Certificates of Coverage and many Summary Plan Descriptions explicitly exclude benefit coverage for medical and surgical

treatment of excessive sweating (hyperhidrosis). The enrollee-specific benefit document must be reviewed to determine what benefits, if any, exist for treatment of hyperhidrosis.

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

BACKGROUND

There are seven serologically distinct forms of botulinum toxin, A through G. All seven neurotoxins share a common structure consisting of one heavy chain and one light chain. They all inhibit acetylcholine release at the neuromuscular junction via the enzymatic inactivation of a protein that is required for the docking and fusion process involved in the release of acetylcholine. Each neurotoxin works at a distinct site. Botulinum toxin type A cleaves the protein SNAP-25 and botulinum toxin type B cleaves synaptobrevin, both of these proteins are part of a protein complex necessary for proper docking and fusion.[1,2,81,288]

The potency units of botulinum toxins are specific to the preparation and assay method utilized. They are not interchangeable and, therefore, the units of biological activity cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.[1,2,81,288]

CLINICAL EVIDENCE

Acquired nystagmus:
The use of BTX-A for the treatment of acquired nystagmus was studied in an open-label trial involving 6 patients.[18] These patients received a total of 17 injections and in each case distance visual acuity improved both subjectively and objectively. Eye movement recordings demonstrated a significant reduction in the amplitude but not the frequency of the oscillations. In another open-label trial, 12 patients with acquired nystagmus received a total of 72 injections of BTX-A.[19] Objective improvements in visual acuity occurred in 8 of the 12 patients and an additional 2 patients reported subjective improvements. In an open-label trial, 3 patients with acquired nystagmus were injected with BTX-A.[20] The injections either abolished or reduced the components of the nystagmus in the treated eye in each individual. Visual acuity improved in one patient, was unchanged in another and worsened in the third patient. Each patient experienced side effects from the BTX-A injection and none elected to continue with the treatment. Another report[172] of two patients with acquired nystagmus were injected with 25 units of botulinum A toxin into the retrobulbar space of one eye. Visual acuity improved in one patient and both experienced improvements in ability to read and watch television, with improvements lasting 5 to 13 weeks. Two patients with acquired pendular nystagmus received botulinum in the horizontal rectus muscle of the right eye.[173] The horizontal component of the nystagmus was eliminated for approximately 2 months and a small improvement of vision occurred. In one patient, the horizontal component of nystagmus increased in the non-injected eye. Neither patient elected further botulinum injections.

Chronic low back pain:
In a randomized, double-blind, placebo controlled trial, the efficacy of BTX-A was studied in the treatment of 31 patients with chronic low back pain.[60] Patients received 5 injections of 40 U BTX-A or placebo at 5 lumbar or 5 lumbosacral sites on the side with pain. Efficacy measures included a Visual Analog Scale (VAS) to measure low back pain intensity and the Oswestry Low Back Pain Questionnaire (OLBPQ) which consists of 10 subsets of questions which deal with pain and activities of daily living. A significant response on the VAS was considered to be a 50% or greater reduction in pain and for the OLBPQ, at least a 2-grade improvement in one or more functional areas in addition to the pain subset. At 3 weeks, 73% of the BTX-A group had >50% pain relief compared to 25% in the placebo group ($p = 0.012$). At 8 weeks, 60% of the BTX-A group vs. 12.5% of the placebo group experienced >50% pain relief ($p = 0.009$). At 8 weeks, 66.7% of the BTX-A group and 18.8% of the placebo group showed improvements in OLBPQ ($p = 0.011$). While this study yielded positive results, it is important to note that the pathology of the back pain was mixed and the patient population was small. Based upon this single Class II study, the American Academy of Neurology (AAN) concluded that botulinum neurotoxin (BoNT) is possibly effective for the treatment of chronic predominantly unilateral low back pain (Level C). However, the panel stated that larger randomized-placebo controlled studies with a homogenous subject population must occur to define the role, if any, of BTX-A in the treatment of chronic low back pain.[138]

Head tremor:
In a double-blind, placebo-controlled, cross-over trial, the effects of botulinum toxin type A (BTX-A) in 10 patients with essential head tremor was assessed.[14] Patients were assessed 2, 4, and 8 weeks after the injections. There was moderate to marked objective improvement in 5 patients after BTX-A injection and in 1 after placebo. Subjective improvements occurred in 5 patients after BTX-A and 3 patients after placebo. Neither the objective nor subjective improvements were statistically significant. In an open-label trial, 43 patients with head tremor (29 with tremulous cervical dystonia and 14 without dystonia) were treated with BTX-A.[15] Patients were assessed clinically using the Tsui scale and a 4 point pain scale. Patients were assessed quantitatively with a bidirectional accelerometer. Significant improvements were found 2 to 3 weeks post injection in the Tsui scale ($p<0.001$) and the pain scale ($p<0.05$) for both sets of patients. The amplitudes of the tremors were reduced significantly ($p<0.05$) although the frequency was unchanged compared to baseline values in both groups.

Motor tics:
In a double-blind, crossover trial, 18 patients with simple motor tics were randomized to treatment with either BTX-A or placebo.[62] Variable doses of BTX-A were injected into the muscle that was suspected to be involved in the motor tic. The dose used was similar to doses used in the treatment of the suspected muscle in other movement disorders. The primary outcome measure was the proportional change in the number of tics per minute at week 2 vs. baseline. Secondary measures included the Shapiro Tourette Syndrome Severity Scale scores, premonitory and urge sensation scores (range 0 - 4). At 2 weeks, BTX-A treatment resulted in a 39% reduction in tics vs. a 5.8% increase with placebo (net effect 37% reduction with BTX-A, $p=0.0007$). BTX-A resulted in a 0.46 point reduction in urge score vs. 0.49 point increase with placebo (net effect 0.94, $p=0.02$). No other measures were statistically significantly different. In a study of 35 patients injected with 115 sessions of botulinum toxin A in the most problematic site of their tics, the mean peak effect was 2.8 on a 0 to 4 clinical rating scale (0, no improvement, to 4, marked improvement in both severity and function). The mean latency to onset of benefit was 3.8 days (maximum, 10 days). Twenty-one (84%) of 25 patients with premonitory sensations noted benefit for these symptoms.[189] The results from these two studies are insufficient to determine botulinum toxin's efficacy in the treatment of tics.

Chronic daily headache:
Four studies were published in the American Academy of Neurology's 2008 assessment of

botulinum neurotoxin for pain disorders.[138] Each of the studies specifically referenced chronic daily headache (CDH) and had a large population of patients with transformed migraine. The primary outcome measure for all the studies was mean change in headache-free days per month. The first study, which used a technique of modifying injection site based on location of pain, showed a significant benefit (11 days vs. 8 days) in the BoNTA treated population.[179] The second study, the largest of patients with CDH, was a randomized, double-blind, placebo-controlled, phase II study, enrolling 702 patients.[135] This trial used a fixed-site strategy. Eligible patients were injected with BoNTA at 225 U, 150 U, 75 U, or placebo and returned for additional masked treatments at day 90 and day 180. Patients were assessed every 30 days for 9 months. The primary efficacy end point was the mean change from baseline in the frequency of headache-free days at day 180 for the placebo nonresponder group. The primary efficacy end point was not met. Mean improvements from baseline at day 180 of 6.0, 7.9, 7.9, and 8.0 headache-free days per month were observed with BoNTA at 225 U, 150 U, 75 U, or placebo, respectively (p=0.44). However, a priori-defined analysis of headache change from baseline in headache frequency revealed that the 225 U and 150 U Botox A groups had statistically significant greater reductions in headache frequency compared with placebo at day 240 (p=0.03). In conclusion, BoNTA was safe and well tolerated. Although the primary efficacy end point was not met, all groups responded to treatment. The 225 U and 150 U groups experienced a greater decrease in headache frequency than the placebo group at day 240, but the placebo response was higher than expected. The third study was a subgroup of patients not taking prophylactic medications from a larger overall study.[133,134] Only this subgroup showed a significant mean increase in headache-free days although there was a decrease in the frequency per 30 days. An additional study evaluated 82 patients with chronic daily headache treated with botulinum neurotoxin A.[188] 76.1% of the chronic migraine patients and 36.4% of the chronic tension-type headache patients were considered responders. Because studies of botulinum A for the prevention of chronic daily headache show mixed results, further studies are recommended.

Tension headache:
Four studies of patients with tension-type headache were reviewed in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders.[138] Patients in these studies were randomized to either botulinum neurotoxin (BoNT) or placebo. After 6 weeks, the first study (n = 112) showed no significant difference compared to a baseline 6 week period in the primary outcome measure of area under the headache curve in the subjects' headache diary.[129] In another of the studies, both the BoNT and the placebo group showed improvement in the primary outcome of mean change from baseline in number of headache-free days from 30 to 60 after injection, but BoNT was not more beneficial and a power analysis was not provided.[174] A third study showed no significant benefit of BoNT after 12 weeks for decrease of headache, intensity on visual analog scale, mean number of headache days, headache hours per day, days on which symptomatic treatment was taken, number of analgesics taken per day, or patient's assessment of improvement.[175] The fourth study, a smaller trial, included 16 patients in a prospective double-blind, placebo-controlled crossover study and thirty patients in an open-label long-term study.[127] These patients showed reduction in headache severity and pericranial muscle tenderness, and increased headache-free days with botulinum treatment.

In a double-blind, placebo-controlled trial BTX-A was studied in the treatment of tension headache in 21 patients.[32] Efficacy measures included analgesic consumption, pain intensity, site and duration of headache, impression of improvement on a clinical global impression scale (CGI), muscle tenderness and pain, and quality of life surveys. These were assessed at baseline and again 4, 8, and 12 weeks post-injection. Improvement from baseline was noted in both the BTX-A and placebo groups in pain intensity and the CGI, but no statistically significant differences were noted between groups. The only statistically significant difference between groups was in the Everyday-Life Questionnaire that found significant differences in favor of placebo at 4 weeks (p=0.047) and 12 weeks (p=0.009). In another double-blind, placebo-controlled trial the efficacy of BTX-A was assessed in the treatment of chronic headache due to a whiplash injury.[33] Outcome

measures were assessed at baseline and 2 and 4 weeks post-injection and included subjective head pain based on visual analog scales and an objective assessment of range of motion. At baseline patients randomized to the BTX-A group had significantly higher pain scores than the placebo group (6.5 vs. 3.0, p<0.01). At 2 weeks there was a trend toward improvement in both measures in the BTX-A group but no change in the placebo group. At 4 weeks, the BTX-A showed significant improvements vs. baseline in pain scores (6.5 vs. 3.5, p<0.01) and range of motion (312 degrees vs. 343 degrees, p<0.01). It was not reported if there were any significant differences between BTX-A and placebo at any time.

In a double-blind, randomized trial the efficacy of BTX-A was compared to placebo in the treatment of tension headaches in 60 patients.[61] At randomization, each patient completed the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) and was asked to record the intensity of headache, daily activities, feelings of depression, tension and anger on a self-rating visual analog scale (VAS). After 4 weeks, patients again completed the WHYMPI and received bilateral injections in the frontal muscles and temporal superficial muscles with either 20 U BTX-A or placebo per injection. The primary efficacy measure was the pain severity ratings from both the WHYMPI and VAS. No statistically significant difference could be found between the groups using either measure. There was no statistically significant difference in the percentage of patients who responded to treatment, defined as a 25% reduction in pain intensity, between the groups. The only statistically significant difference between the groups was found at 4 weeks in the affective score on WHYMPI and angry mood on the VAS.

In another randomized, double-blind trial, the safety and efficacy of BTX-A was compared to placebo in the treatment of chronic tension-type headache.[103] Thirty-seven patients were randomized to receive 100 units of BTX-A (n = 22) or placebo (n=15) injected into the temporal and cervical muscles in each side of the head. Patients kept a daily diary beginning 1 month prior to injection and for 3 months post injection. Headache intensity, rated on a 6 point scale, analgesic use, and any other pertinent information related to headaches was recorded. After treatment, the BTX-A group showed steady, statistically significant improvements in headache severity over the 3 months of the study (p=0.002). At 3 months the BTX-A group had a significant improvement in the number of headache free days compared to the baseline period (p=0.001). There also was a numerically greater number of patients treated with BTX-A that had a greater than 25% improvement in headache symptoms scores (13/22 vs. 2/15 in the placebo group, no p value given). No serious side effects were reported during the trial.

Additional small randomized controlled trials have found conflicting results similar to those presented above.[128,176-8] Until larger randomized trials are conducting showing a beneficial effect of BTX-A, its use in tension headache is unproven.

Migraine headache:
Four studies of patients with episodic migraines treated with BoNT were published in the American Academy of Neurology's 2008 assessment of botulinum neurotoxin for pain disorders.[138] One randomized, double-blind study included 232 patients with four to eight moderate to severe migraines per month. This study compared BoNTA to placebo and was powered to detect a difference of 2 headaches per month difference between groups. A statistical significance was not seen between the groups at 1 to 3 months after injection.[168]

The second study included 3 sequential controlled investigations with re-randomization of 418 patients with a dosing range of 7.5 to 50 units. Patients' baseline was four to eight moderate to severe migraines per month. Both BoNTA and placebo produced a comparable result in decrease from baseline in frequency between 1 to 4 months. There were no statistically significant, consistent, between group differences.[169]

The third study was a double-blind, vehicle-controlled study of 123 patients with a history of 2 to 8

moderate to severe headaches per month.[34] Patients were randomized to vehicle only, 25 U BTX-A, or 75 U BTX-A. During a 1 month baseline period and for 3 months post-injection, patients recorded in a daily diary migraine frequency, severity and associated symptoms. There were statistically significant improvements in the BTX-A 25 U group vs. vehicle in the reduction of moderate to severe migraine headaches at 2 months (-1.57 vs. -0.37, p=0.008) and 3 months (-1.88 vs. -0.98, p=0.042) and in all migraines at 3 months (-2.12 vs. -0.9, p=0.014). There were also significantly more patients who had 2 few migraines per month and more patients had at least a 50% reduction in the frequency of migraines at 3 months in the 25 U BTX-A group vs. vehicle. At months 1 and 2, the 25U group had significant improvement in the severity of migraine headaches and at month 3 experienced fewer migraine-associated symptoms than the vehicle group. At month 2 both the 25 U and 75 U BTX-A had significant improvements in Subject Global Assessment scores vs. vehicle (BTX-A 25 U, 1.19; BTX-A 75 U, 1.25; vehicle 0.46; p<0.041).

The fourth study, a double-blind, randomized, placebo-controlled study, included sixty patients with migraine according to criteria of the International Headache Society.[132] The patients were randomly assigned to receive either placebo in the frontal and neck muscles, or to receive 16 U botulinum toxin A in the frontal muscles and placebo in the neck muscles, or to receive a total of 100 U botulinum toxin A in the frontal and neck muscles. The observational period was 3 months. In both treatment groups, 30% of patients showed a reduction of migraine frequency in month 3 by at least 50% compared with baseline, in the placebo group 25% of the patients showed such a reduction (P=0.921). There were no significant differences between the three study groups with respect to reduction of migraine frequency, number of days with migraine, and the number of total single doses to treat a migraine attack. In the post hoc analysis, the reduction of all accompanying symptoms was significantly higher in the 16 U treatment group compared with the placebo group. A significantly higher number of adverse events occurred in the 100 U treatment group compared with the placebo group. All adverse events were mild and transient. This study did not show any efficacy of botulinum toxin A in the prophylactic treatment of migraine.

Other migraine studies included an open-label trial in which 106 patients with migraine headache were treated with BTX-A.[35] Patients enrolled either had received BTX-A injections for hyper-functional facial lines or sought treatment with BTX-A for migraine headaches. Of the 106 patients, 77 were classified as having migraine headaches according to the International Headache Society Criteria for Migraine. In the 77 patients with migraine headache treated prophylactically, 51% had complete resolution of their headaches. Patients with less frequent headaches or less severe headaches tended to have complete resolution of their headaches more often than those with higher frequency or severity. Ten subjects with an acute migraine headache were treated with BTX-A and 7 had complete resolution of their headaches in 1 to 2 hours. In another open label trial, 24 of 29 patients who were injected with BTX-A in the corrugator supercilii muscles had a beneficial effect on their migraine headaches.[131]

Two additional randomized, double-blind, placebo-controlled exploratory studies (n=495 and n=369) of botulinum toxin type A in the treatment of episodic migraine showed no statistically significant difference in improvement versus placebo.[170-1] Other small studies utilizing botulinum toxin for migraine have been conducted.[180-7]

A meta-analysis of eight randomized, double-blind, placebo-controlled trials also concluded that botulinum toxin A for the prophylactic treatment of episodic migraine headaches was not significantly different from placebo, both from a clinical and statistical perspective.[281]

Miscellaneous:
Botulinum toxin A has been studied in a number of other disorders including: cricopharyngeal dysphagia,[42,64-5,148-64] gustatory epiphora (crocodile tears),[48,77,193-5] Sphincter of Oddi dysfunction,[50,102,200-3] pancreas divisum,[72] anismus,[51,78,139,140] lower urinary tract dysfunction,[71,88,122-3,146] pelvic floor spasticity,[71,146] chronic prostatic pain,[53] severe paradoxical

vocal cord movement,[55,204] postparotidectomy sialoceles,[56] severe bruxism,[57,80,205-12] temporomandibular disorders,[58,213-25,243] myofascial pain syndrome,[59,75,96,226-36] brachial plexus palsy,[69,70,237-8] thyroid associated ophthalmopathy,[73,239-42] esophageal spasm,[74,190-1] post-thoracotomy pseudoangina,[75] epiphora following salivary gland transplantation,[77] trigeminal neuralgia,[293-295] trismus and stridor in amyotrophic lateral sclerosis,[79,245] proctalgia fugax,[82] nasal hypersecretion,[83,247,284] gastroparesis (including diabetic gastroparesis),[89,90,98,145,270-7] Lichen simplex,[94] lateral epicondylitis,[95,248-51] Stiff-person syndrome,[97,254] benign prostatic hyperplasia,[109,130,146,285] traumatic sixth nerve palsy,[91,256-9] Tourette's syndrome,[124,189,261-4] and pain and/or wound healing after hemorrhoidectomy.[125,265-6] The studies in these disorders have been small and/or uncontrolled open-label trials. Larger, well-designed studies must occur to demonstrate the effectiveness of botulinum toxin in the treatment of these conditions.

Technology Assessments:
A 2011 Cochrane review was published evaluating botulinum toxin injections for low back pain and sciatica.[298] Authors included three randomized trials (n=123 patients). Only one study included patients with chronic non-specific LBP; the other two examined unique subpopulations. Only one of the three trials had a low risk of bias and demonstrated that BoNT injections reduced pain at three and eight weeks and improved function at eight weeks better than saline injections. The second trial showed that BoNT injections were better than injections of corticosteroid plus lidocaine or placebo in patients with sciatica attributed to piriformis syndrome. The third trial concluded that BoNT injections were better than traditional acupuncture in patients with third lumbar transverse process syndrome. Both studies with high risk of bias had several key limitations. Heterogeneity of the studies prevented meta-analysis. There is low quality evidence that BoNT injections improved pain, function, or both better than saline injections and very low quality evidence that they were better than acupuncture or steroid injections. Future trials should standardize patient populations, treatment protocols and comparison groups, enlist more participants and include long-term outcomes, cost-benefit analysis and clinical relevance of findings.

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for chronic tension-type headache dated December 30, 2011.[299] A relatively large number of well-designed, randomized, placebo-controlled trials (RCTs) have evaluated the effects of botulinum toxin A (BTX-A) on patients diagnosed with chronic tension-type headache (CTTH). The majority of these studies found no benefit of BTX-A relative to placebo. The two studies that did report beneficial effects of BTX on headache frequency and intensity were very small. Overall, BTX-A was safe. None of the studies compared BTX-A with other prophylactic treatments for CTTH. An annual review of the Hayes Directory on January 1, 2014 resulted in no changes to the original findings.

Hayes compiled a Medical Technology Directory on botulinum toxin treatment for migraine headache dated September 22, 2011.[296] Although a relatively large number of well-designed randomized controlled trials (RCTs) have evaluated onabotulinumtoxinA (onaBTX-A) and abobotulinumtoxinA (aboBTX-A) [BTX-A] for prevention of migraine, the clinical role of this treatment remains to be established. Many of the available placebo-controlled RCTs found that BTX-A did not provide statistically significant benefits or found that the benefits obtained were inconsistent, for instance, occurring at some time points but not at others. In contrast, the largest available RCT and one of the older RCTs found that patients who underwent treatment with onaBTX-A experienced statistically significant improvements such as reductions in migraine frequency and severity. This divergence in study results cannot be resolved based solely on differences in study size and a more likely explanation was that the benefits obtained with onaBTX-A were relatively small, perhaps too small to be clinically significant. Moreover, due to lack of long-term follow-up, the available RCTs do not provide any data concerning the durability of potential benefits from treatment with onaBTX-A. In addition, there was insufficient evidence to support conclusions regarding the efficacy of onaBTX-A relative to other types of medication for prevention of migraine. Likewise, there was very limited evidence regarding the effectiveness of

aboBTX-A, and no evidence regarding other types of BTX, for the management of chronic or recurrent headache. Therefore, Hayes has assigned a D rating (no proven benefit and/or not safe) to abobotulinumtoxinA for prevention of migraine and to rimabotulinumtoxinB as a treatment for migraine headache. Overall, onaBTX-A was safe with few serious complications reported, earning onabotulinumtoxinA a Hayes rating of C (potential but unproven benefit) for prevention of migraine headache. Further studies are needed to determine the clinical role of BTX-A relative to current treatments for prevention of migraine. An annual review of the Hayes Directory on October 15, 2013 resulted in no changes to the original findings.

Hayes has compiled a Medical Technology Directory on trigger point injections (TPI) for myofacial pain on December 24, 2013. The literature search identified a total of 17 peer-reviewed randomized controlled studies comparing TPIs with placebo or an active control. Based upon these findings, the investigators concluded that TPIs improve pain and may improve function temporarily in patients with myofascial pain, but these effects appear to be unrelated to the substance that is injected. TPI with local anesthetics improves pain compared with no treatment, but not compared with placebo TPI, suggesting that the injection procedure itself and/or patient expectations rather than the anesthetic provide pain relief.[290]

Professional Societies:
In 2008, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology published evidence-based (studies classified as Class I to IV and recommendations classified as levels A to U)[286] assessments on the use of botulinum neurotoxin in the treatment of autonomic disorders and pain,[138] movement disorders,[147] and spasticity.[196] The Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society also published an evidence-based review of the pharmacologic treatment of spasticity in children and adolescents with cerebral palsy in 2010.[21] Recommendations from these reviews are:

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

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

For non-cosmetic use, onabotulinumtoxinA (Botox) is FDA approved for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer). Safety and effectiveness of onabotulinumtoxinA (Botox) have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month).[1]

OnabotulinumtoxinA is also approved for treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor dititorum sublimis). It is also indicated for reducing the severity of abnormal head position and neck pain associated with cervical dystonia in adults; for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above; for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response or are intolerant to an anticholinergic medication; for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication; and for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.[1]

RimabotulinumtoxinB (Myobloc) is FDA approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.[2]

For non-cosmetic use, abobotulinumtoxinA (Dysport) is FDA approved for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients.[81]

IncobotulinumtoxinA (Xeomin) is FDA approved for the treatment of adults with cervical dystonia to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients. IncobotulinumtoxinA is also indicated for the treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA (Botox).[288]

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document

HCPCS Code	Description
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

ICD-9 Code	Description
333.6	Genetic torsion dystonia
333.71	Athetoid cerebral palsy
333.79	Other acquired torsion dystonia
333.81	Blepharospasm
333.82	Orofacial dyskinesia

333.83	Spasmodic torticollis
333.84	Organic writers' cramp
333.89	Other fragments of torsion dystonia
342.10	Spastic hemiplegia affecting unspecified side
342.11	Spastic hemiplegia affecting dominant side
342.12	Spastic hemiplegia affecting nondominant side
343.0	Diplegic infantile cerebral palsy
343.1	Hemiplegic infantile cerebral palsy
343.2	Quadriplegic infantile cerebral palsy
343.3	Monoplegic infantile cerebral palsy
343.4	Infantile hemiplegia cerebral palsy
343.8	Other specified infantile cerebral palsy
343.9	Unspecified infantile cerebral palsy
344.61	Cauda equine syndrome with neurogenic bladder
346.70	Chronic migraine without aura, without mention of intractable migraine without mention of status migrainosus (without mention of refractory migraine without mention of status migrainosus)
346.71	Chronic migraine without aura, with intractable migraine, so stated, without mention of status migrainosus (with refractory migraine, so stated, without mention of status migrainosus)
346.72	Chronic migraine without aura, without mention of intractable migraine with status migrainosus (without mention of refractory migraine with status migrainosus)
346.73	Chronic migraine without aura, with intractable migraine, so stated, with status migrainosus (with refractory migraine, so stated, with status migrainosus)
351.0	Bell's palsy
351.1	Geniculate ganglionitis
351.8	Other facial nerve disorders
351.9	Facial nerve disorder, unspecified
355.0	Lesion of sciatic nerve
378.73	Strabismus in other neuromuscular disorders
378.82	Spasm of conjugate gaze
478.75	Laryngeal spasm
527.7	Disturbance of salivary secretion
530.0	Achalasia and cardiospasm
564.6	Anal spasm
565.0	Anal fissure
596.51	Hypertonicity of bladder
596.54	Neurogenic bladder, NOS
596.55	Detrusor sphincter dyssynergia
705.21	Primary focal hyperhidrosis
705.22	Secondary focal hyperhidrosis
724.3	Sciatica
781.0	Abnormal involuntary movements
781.93	Ocular torticollis
784.40	Voice and resonance disorder, unspecified
784.42	Dysphonia
788.31	Urge incontinence
788.33	Mixed incontinence, (male) (female)
951.4	Injury to facial nerve (seventh cranial nerve)

ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2015***, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. **The effective date for ICD-10 code set implementation is subject to change.*

ICD-10 Diagnosis Code (Effective 10/01/15)	Description
G24.1	Genetic torsion dystonia
G24.09	Other drug induced dystonia
G24.2	Idiopathic nonfamilial dystonia
G24.3	Spasmodic torticollis
G24.4	Idiopathic orofacial dystonia
G24.5	Blepharospasm
G24.8	Other dystonia
G24.9	Dystonia, unspecified
G25.89	Other specified extrapyramidal and movement disorders
G43.701	Chronic migraine without aura, not intractable, with status migrainosus
G43.709	Chronic migraine without aura, not intractable, without status migrainosus
G43.711	Chronic migraine without aura, intractable, with status migrainosus
G43.719	Chronic migraine without aura, intractable, without status migrainosus
G51.0	Bell's palsy
G51.1	Geniculate ganglionitis
G51.2	Melkersson's syndrome
G51.3	Clonic hemifacial spasm
G51.4	Facial myokymia
G51.8	Other disorders of facial nerve
G51.9	Disorder of facial nerve, unspecified
G57.00	Lesion of sciatic nerve, unspecified lower limb
G57.01	Lesion of sciatic nerve, right lower limb
G57.02	Lesion of sciatic nerve, left lower limb
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G80.3	Athetoid cerebral palsy
G80.4	Ataxic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified
G81.10	Spastic hemiplegia affecting unspecified side
G81.11	Spastic hemiplegia affecting right dominant side
G81.12	Spastic hemiplegia affecting left dominant side
G81.13	Spastic hemiplegia affecting right nondominant side
G81.14	Spastic hemiplegia affecting left nondominant side
G83.4	Cauda equina syndrome
H50.89	Other specified strabismus
H51.0	Palsy (spasm) of conjugate gaze
J38.5	Laryngeal spasm
K11.7	Disturbances of salivary secretion
K22.0	Achalasia of cardia
K59.4	Anal spasm

K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified
L74.510	Primary focal hyperhidrosis, axilla
L74.511	Primary focal hyperhidrosis, face
L74.512	Primary focal hyperhidrosis, palms
L74.513	Primary focal hyperhidrosis, soles
L74.519	Primary focal hyperhidrosis, unspecified
L74.52	Secondary focal hyperhidrosis
M54.30	Sciatica, unspecified side
M54.31	Sciatica, right side
M54.32	Sciatica, left side
M54.40	Lumbago with sciatica, unspecified side
M54.41	Lumbago with sciatica, right side
M54.42	Lumbago with sciatica, left side
N31.0	Uninhibited neuropathic bladder, not elsewhere classified
N31.1	Reflex neuropathic bladder, not elsewhere classified
N31.9	Neuromuscular dysfunction of bladder, unspecified
N32.81	Overactive bladder
N36.44	Muscular disorders of urethra
N39.41	Urge incontinence
N39.46	Mixed incontinence
R25.0	Abnormal head movements
R25.1	Tremor, unspecified
R25.2	Cramp and spasm
R25.3	Fasciculation
R25.8	Other abnormal involuntary movements
R25.9	Unspecified abnormal involuntary movements
R29.891	Ocular torticollis
R49.0	Dysphonia
R49.9	Unspecified voice and resonance disorder
S04.50XA	Injury of facial nerve, unspecified side, initial encounter
S04.51XA	Injury of facial nerve, right side, initial encounter
S04.52XA	Injury of facial nerve, left side, initial encounter

REFERENCES

1. Botox [prescribing information]. Irvine, CA: Allergan Pharmaceuticals, Inc., February 2014.

2. Myobloc [prescribing information]. South San Francisco, CA: Solstice Neurosciences, Inc., May 2010.

3. Bell MS, Vermeulen LC, Sperling KB. Pharmacotherapy with botulinum toxin: Harnessing nature's most potent neurotoxin. Pharmacotherapy. 2000;20(9):1079-91.

4. Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. J Neurol Neurosurg Psychiatry. 1990;53(8):633-639.

5. Blitzer A, Brin MF, Greene PE, Fahn S. Botulinum toxin injection for the treatment of oromandibular dystonia. Ann Otol Rhinol Laryngol. 1989;98(2):93-7.

6. Hermanowicz N, Truong DD. Treatment of oromandibular dystonia with botulinum toxin. Laryngoscope. 1991;101(11):1216-18.

7. Jankovic J. Treatment of dystonia. Lancet Neurol. 2006;5(10):864.

8. Elmiyeh B, Prasad VM, Upile T, et al. A single-centre retrospective review of unilateral and bilateral Dysport injections in adductor spasmodic dysphonia. Logoped Phoniatr Vocol. 2010;35(1):39-44.

9. Truong DD, Bhidayasiri R. Botulinum toxin therapy of laryngeal muscle hyperactivity syndromes: comparing different botulinum toxin preparations. Eur J Neurol. 2006;13(Suppl 1):36-41.

10. Upile T, Elmiyeh, Jerjes W, et al. Unilateral versus bilateral thyroartytenoid botulinum toxin injections in adductor spasmodic dysphonia: a prospective study. Head Face Med. 2009;5:20.

11. Van den Bergh P, Francart J, Mourin S, et al. Five-year experience in the treatment of focal movement disorders with low dose Dysport botulinum toxin. Muscle and Nerve. 1995;18(7):720-9.

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

13. Trosch RM, Pullman SL. Botulinum toxin A injections for the treatment of hand tremors. Mov Disord. 1994;9(6):601-9.

14. Pahwa R, Busenbark K, Swanson-Hyland EF, et al. Botulinum toxin treatment of essential head tremor. Neurology. 1995;45(4):822-4.

15. Wissel J, Masuhr F, Schelosky L, et al. Quantitative assessment of botulinum toxin treatment in 43 patients with head tremor. Mov Disord. 1997;12(5):722-6.

16. Hertegard S, Granqvist S, Lindestad P. Botulinum toxin injections for essential voice tremor. Ann Oto Rhinol Laryngol. 2000;109(2):204-9.

17. Warrick P, Dromey C, Irish JC, et al. Botulinum toxin for essential tremor of the voice with multiple anatomical sites of tremor: A crossover design study of unilateral versus bilateral injection. Laryngoscope. 2000;110(8):1366-74.

18. Repka MX, Savino PJ, Reinecke RD. Treatment of acquired nystagmus with botulinum neurotoxin A. Arch Ophthalmol. 1994;112(10):1320-4.

19. Ruben ST, Lee JP, O'Neil D, et al. The use of botulinum toxin for treatment of acquired nystagmus and oscillopsia. Ophthalmology. 1994;101(4):783-7.

20. Tomsak RL, Remler BF, Averbuch-Heller L, et al. Unsatisfactory treatment of acquired nystagmus with retrobulbar injection of botulinum toxin. Am J Ophthalmol. 1995;119(4):489-96.

21. 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.

22. Bakheit AM, Severa S, Cosgrove A, et al. Safety profile and efficacy of botulinum toxin A (Dysport) in children with muscle spasticity. Dev Med Child Neurol. 2001;43(4):234-8.

23. Corry IS, Cosgrove AP, Walsh EG, et al. Botulinum toxin A in the hemiplegic upper limb: a double blind trial. Dev Med Child Neurol. 1997;39(3):185-93.

24. Suputtitada A, Suwanwela NC. The lowest effective dose of botulinum A toxin in adult patients with upper limb spasticity. Disabil Rehabil. 2005;27(4):176-84.

25. Arroyo A, Perez F, Serrano P, et al. Surgical versus chemical (botulinum toxin) sphincterotomy for chronic anal fissure: long-term results of a prospective randomized clinical and manometric study. Am J Surg. 2005;189(4):429-34.

26. American Gastroenterological Association. AGA medical position statement: Diagnosis and care of patients with anal fissure. Gastroenterology 2003;123:233-4.

27. De Nardi P, Ortolano E, Radaelli G, Staudacher C. Comparison of glycerine trinatrate and botulinum toxin-A for the treatment of chronic anal fissure: long-term results. Diseases of the Colon and Rectum. 2006;49(4):427-32.

28. Iswariah H, Stephens J, Rieger N et al. Randomized prospective controlled trial of lateral internal sphincterectomy versus injection of botulinum toxin for the treatment of idiopathic fissure in ano. Anz J Surg. 2005;75(7):553-5.

29. Brisinda G, Cadeddu F, Brandara F, et al. Randomized clinical trial comparing botulinum toxin injections with 0.2 per cent nitroglycerin ointment for chronic anal fissure. Br J Surg. 2007;94(2):162-7.

30. Brisinda G, Cadeddu F, Brandara F, et al. Botulinum toxin for recurrent anal fissure following lateral internal sphincterotomy. Br J Surg. 2008;95(6):774-8.

31. Allescher HD, Storr M, Seige M, et al. Treatment of achalasia: botulinum toxin injection vs. pneumatic balloon dilation. A prospective study with long-term follow-up. Endoscopy. 2001; 33(12):1007-17

32. Rollnik JD, Tanneberger O, Schubert M, et al. Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study. Headache. 2000;40(4):300-5.

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

34. Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. Headache. 2000;40(6);445-50.

35. Binder WJ, Brin MF, Blitzer A, et al. Botulinum toxin type A (Botox) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg. 2000;123(6):669-76.

36. Brisinda G, Albanese A, Cadeddu F, et al. Botulinum neurotoxin to treat chronic anal fissure: results of a randomized "Botox vs. Dysport" controlled trial. Aliment Pharmacol Ther. 2004 Mar 15;19(6):695-701.

37. American Gastroenterological Association. AGA Technical Review on the Diagnosis and Care of Patients with Anal Fissure. Gastroenterology 2003;123:235-45.

38. Pasricha PJ, Ravich WJ, Hendrix TR, et al. Intrasphincteric botulinum toxin for the treatment of achalasia. N Engl J Med. 1995;332(12):774-8.

39. Fishman VM, Parkman HP, Schiano TD, et al. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. Am J Gastroenterol. 1996;91(9):1724-30.

40. Pasricha PJ, Rai R, Ravich WJ, et al. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology. 1996;110(5):1410-1415.

41. Gordon JM, Eaker EY. Prospective study of esophageal botulinum toxin injection in high-risk achalasia patients. Am J Gastroenterol. 1997;92(10):1812-1817.

42. Alberty J, Oelerich M, Ludwig K, et al. Efficacy of botulinum toxin A for treatment of upper esophageal sphinter dysfunction. Laryngoscope. 2000;110(7):1151-1156.

43. Marconi, R, Sabatino A, Chiacchiari L, Montagano T,. Botulinum toxin in writing tremor. Movement Disorders. 1995;10(3):403, Number 113.

44. Annese V, Bassotti G, Coccia G, et al. Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia. Aliment Pharmacol Ther. 1999;13(10):1347-50.

45. Hartl DM, Julieron M, LeRidant AM, et al. Botulinum toxin A for quality of life improvement in post-parotidectomy gustatory sweating (Frey's syndrome). J Laryngol Otol. 2008;122(10):1100-4.

46. Laccourreye O, Akl E, Gutierrez-Fonseca R, et al. Recurrent gustatory sweating (Frey syndrome) after intracutaneous injection of botulinum toxin type A. Incidence, management and outcome. Arch Otolaryngol Head Neck Surg. 1999;125(3):283-286.

47. von Lindern JJ, Niederhagen B, Berge S, et al. Frey syndrome: Treatment with type A botulinum toxin. Cancer. 2000;89(8):1659-1663.

48. Hofmann RJ. Treatment of Frey's syndrome (gustatory sweating) and 'crocodile tears' (gustatory epiphora) with purified botulinum toxin. Ophthalmic Plast Reconstr Surg. 2000;16(4):289-291.

49. Yablon SA, Agana BT, Ivanhoe CB, Boake C. Botulinum toxin in severe upper extremity spasticity among patients with traumatic brain injury: An open-labeled trial. Neurology. 1996;47(4):939-944.

50. Wehrmann T, Seifert H, Seipp M, et al. Endoscopic injection of botulinum toxin for biliary sphincter of Oddi dysfunction. Endoscopy. 1998;30(8):702-707.

51. Joo JS, Agachan F, Wolff B, et al. Initial North American experience with botulinum toxin type A for the treatment of anismus. Dis Colon Rectum. 1996;39(10):1107-1111.

52. Schurch B, Stohrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000;164(3 Pt 1):692-697.

53. Zermann D, Ishigooka M, Schubert J, Schmidt RA. Perisphincteric injection of botulinum toxin type A. A treatment option for patients with chronic prostatic pain? Eur Urol. 2000;38(4):393-399.

54. Giess R, Naumann M, Werner E, et al. Injections of botulinum toxin A into the salivary glands improve sialorrhea in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry.

2000;69(1):121-123.

55. Maillard I, Schweizer V, Broccard A, et al. Use of botulinum toxin type A to avoid tracheal intubation or tracheostomy in severe paradoxical vocal cord movement. Chest. 2000;118(3):874-877.

56. Vargas H, Galati LT, Parnes SM. A pilot study evaluating the treatment of postparotidectomy sialoceles with botulinum toxin type A. Arch Otolaryngol Head Neck Surg. 2000;126(3):421-424.

57. Tan EK, Jankovic J. Treating severe bruxism with botulinum toxin. J Am Dent Assoc. 2000;131(2):211-216.

58. Freund B, Schwartz M, Symington JM. Botulinum toxin: new treatment for temporomandibular disorders. Br J Oral Maxillofac Surg. 2000;38(5):466-471.

59. Porta M. A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. Pain. 2000;85(1-2):101-105.

60. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain: A randomized, double-blind study. Neurology. 2001;56(10):1290-1293.

61. Schmitt WJ, Slowey E, Fravi N, et al. Effect of botulinum toxin A injections in the treatment of chronic tension-type headache: A double-blind, placebo-controlled trial. Headache. 2001;41(7):658-664.

62. Marras C, Andrews D, Sime E, Lang AE. Botulinum toxin for simple motor tics: A randomized, double-blind, controlled clinical trial. Neurology. 2001:56(5):605-610.

63. Schulte-Baukloh H, Michael T, Schobert J, et al. Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. Urology. 2002;59(3):325-328.

64. Haapaniemi JJ, Laurikainen EA, Pulkkinen J, Marttila RJ. Botulinum toxin in the treatment of cricopharyngeal dysphagia. Dysphagia. 2001;16(3):171-175.

65. Shaw GY, Searl JP. Botulinum toxin treatment for cricopharyngeal dysfunction. Dysphagia. 2001;16(3):161-167.

66. Porta M, Gamba M, Bertacchi G, Vaj P. Treatment of sialorrhoea with ultrasound guided botulinum toxin type A injection in patients with neurological disorders. J Neurol Neurosurg Psychiatry. 2001;70(4):538-540.

67. Pal PK, Calne DB, Calne S, Tsui JKC. Botulinum toxin A as treatment for drooling saliva in PD. Neurology. 2000;54(1):244-247.

68. Ellies M, Laskawi R, Rohrbach-Volland S, et al. Botulinum toxin to reduce saliva flow: selected indications for ultrasound-guided toxin application into salivary glands. Laryngoscope. 2002;112(1):82-86.

69. Rollnik JD, Hierner R, Schubert M, et al. Botulinum toxin treatment of cocontractions after birth-related brachial plexus lesions. Neurology. 2000;55(1):112-114.

70. Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients

with brachial plexus birth palsy. Pediatr Rehabil. 2001;4(1):29-36.

71. Phelan MW, Franks M, Somogyi GT, et al. Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. J Urol. 2001;165(4):1107-1110.

72. Wehrmann T, Schmitt T, Seifert H. Endoscopic botulinum toxin injection into the minor papilla for treatment of idiopathic recurrent pancreatitis in patients with pancreatic divisum. Gastrointest Endosc. 1999;50(4):545-548.

73. Traisk F, Tallstedt L. Thyroid associated ophthalmopathy: botulinum toxin A in the treatment of upper eyelid retraction - a pilot study. Acta Ophthalmol Scand. 2001;79(6):585-588.

74. Storr M, Allescher HD, Rosch T, et al. Treatment of symptomatic diffuse esophageal spasm by endoscopic injections of botulinum toxin: a prospective study with long-term follow-up. Gastrointest Endosc. 2001;54(6):754-759.

75. Diaz JH, Gould HJ. Management of post-thoracotomy pseudoangina and myofascial pain with botulinum toxin. Anesthesiology. 1999;91(3):877-879.

76. Beerens AJ, Snow GB. Botulinum toxin A in the treatment of patients with Frey syndrome. Br J Surg. 2002;89(1):116-119.

77. Keegan DJ, Geerling G, Lee JP, et al. Botulinum toxin treatment for hyperlacrimation secondary to aberrant regenerated seventh nerve palsy or salivary gland transplantation. Br J Ophthalmol. 2002;86(1):43-46.

78. Ron Y, Avni Y, Lukovetski A, et al. Botulinum toxin type-A in therapy of patients with anismus. Dis Colon Rectum. 2001;44(12):1821-1826.

79. Winterholler MG, Heckman JG, Hecht M, Erbguth FJ. Recurrent trismus and stridor in an ALS patient: successful treatment with botulinum toxin. Neurology. 2002;58(3):502-503.

80. Pidcock FS, Wise JM, Christensen JR. Treatment of severe post-traumatic bruxism with botulinum toxin-A: a case report. J Oral Maxillofac Surg. 2002;60(1):115-117.

81. Dysport [prescribing information]. Wrexham, UK: Ipsen Biopharm Ltd., March 2012.

82. Katsinelos P, Kalomenopoulou M, Christodoulou K, et al. Treatment of proctalgia fugax with botulinum A toxin. Eur J Gastroenterol Hepatol 2001;13(11):1371-1373.

83. Rohrbach S, Laskawi R. Minimally invasive application of botulinum toxin type A in nasal hypersecretion. ORL J Otorhinolaryngol Relat Spec. 2001;63(6):382-384.

84. Defazio G, Abbruzzese G, Girlanda P, et al. Botulinum toxin A treatment for primary hemifacial spasm. A 10-year multicenter study. Arch Neurol. 2002;59(3):418-420.

85. Jitpimolmard S, Tiamkao S, Laopaiboon M. Long term results of botulinum toxin type A (Dysport) in the treatment of hemifacial spasm: a report of 175 cases. J Neurol Neurosurg Psychiatry. 1998;64(6):751-757.

86. Yoshimura DM, Aminoff MJ, Tami TA, Scott AB. Treatment of hemifacial spasm with botulinum toxin. Muscle Nerve. 1992;15(9):1045-1049.

87. Mauriello JA, Leone T, Dhillon S, et al. Treatment choices of 119 patients with hemifacial spasm over 11 years. Clin Neurol Neurosurg. 1996;98(3):213-216.

88. Chen JL, Chen CY, Kuo HC. Botulinum toxin A injection to the bladder neck and urethra for medically refractory lower urinary tract symptoms in men without prostatic obstruction. J Formos Med Assoc. 2009;108(12):950-6.

89. Miller LS, Szych GA, Kantor SB, et al. Treatment of idiopathic gastroparesis with injection of botulinum toxin into the pyloric sphincter muscle. Am J Gastroenterol. 2002;97(7):1653-1660.

90. Ezzeddine D, Rajkamal J, Katz N, et al. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc. 2002;55(7):920-923.

91. Kao LY, Chao AN. Subtenon injection of botulinum toxin for treatment of traumatic sixth nerve palsy. J Pediatr Ophthalmol Strabismus. 2003;40(1):27-30.

92. Autti-Ramo I, Larsen A, Taimo A, von Wendt L. Management of the upper limb with botulinum toxin type A in children with spastic cerebral palsy and acquired brain injury: clinical implications. Eur J Neurol 2001;8(suppl 5):136-144.

93. Wilson DJ, Childers MK, Cooke DL, Smith BK. Kinematic changes following botulinum toxin injection after traumatic brain injury. Brain Inj. 1997;11(3):157-167.

94. Heckmann M, Heyer G, Brunner B, Plewig G. Botulinum toxin type A injection in the treatment of lichen simplex: an open pilot study. J Am Acad Dermatol. 2002;46(4):617-619.

95. Keizer SB, Rutten HP, Pilot P, et al. Botulinum toxin injection versus surgical treatment for tennis elbow. A randomized pilot study. Clin Orthop. 2002;401:125-131.

96. Alo KM, Yland MJ, Kramer DL, Charnov JH, Redko V. Botulinum toxin in the treatment of myofascial pain. Pain Clinic. 1997;10:107-116.

97. Davis D, Jabbari B. Significant improvement of Stiff-person syndrome after paraspinal injection of botulinum toxin A. Mov Disord. 1993;8(3):371-373.

98. Lacy BE, Zayat EN, Crowell MD, Schuster MM. Botulinum toxin for the treatment of gastroparesis: a preliminary report. Am J Gastroenterol. 2002;97(6):1548-52.

99. Fishman LM, Anderson C, Rosner B. Botox and physical therapy in the treatment of piriformis syndrome. Am J Phys Med Rehabil. 2002;81(12):936-942.

100. Childers MK, Wilson DJ, Gnatz SM, et al. Botulinum toxin type A use in piriformis muscle syndrome. A pilot study. Am J Phys Med Rehabil. 2002;81(10):751-759.

101. Bothwell JE, Clarke K, Dooley JM, et al. Botulinum toxin A as a treatment for excessive drooling in children. Pediatr Neurol. 2002;27(1):18-22.

102. Murray W, Kong S. Botulinum toxin may predict the outcome of endoscopic sphincterotomy in episodic functional post-cholecystectomy biliary pain. Scand J Gastroenterol. 2010;Feb 15. [Epub ahead of print]

103. Smuts JA, Baker MK, Smuts HM, et al. Prophylactic treatment of chronic tension-type headache using botulinum toxin type A. Eur J Neurol. 1999;6(Suppl 4):99-102.

104. Flanders M, Chin D, Boghen D. Botulinum toxin: preferred treatment for hemifacial spasm. Eur Neurol. 1993;33(4):316-319.

105. Elston JS. The management of blepharospasm and hemifacial spasm. J Neurol. 1992;239(1):5-8.

106. Berardelli A, Formica A, Mercuri B, et al. Botulinum toxin treatment in patients with focal dystonia and hemifacial spasm. A multicenter study of the Italian Movement Disorder Group. Ital J Neurol Sci. 1993;14(5):361-367.

107. Price J, O'Day J. Efficacy and side effects of botulinum toxin treatment for blepharospasm and hemifacial spasm. Aust NZ J Ophthalmol. 1994;22(4):255-260.

108. Cuevas C, Madrazo I, Magallon E, et al. Botulinum toxin-A for the treatment of hemifacial spasm. Arch Med Res. 1995;26(4):405-408.

109. Maria G, Brisinda G, Civello IM, 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):259-265.

110. Schulte-Baukloh H, Michael T, Sturzebecher B, Knispel HH. Botulinum-A toxin detrusor injection as a novel approach in the treatment of bladder spasticity in children with neurogenic bladder. Eur Urol. 2003;44(1):139-143.

111. Riccabona M, Koen M, Schindler M, et a. Botulinum-A toxin injection into the detrusor: A safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflexia. J Urol. 2004;171(2 Pt 1):845-848.

112. Lipp A, Trottenberg T, Schink T, et al. A randomized trial of botulinum toxin A for treatment of drooling. Neurology. 2003;61(9):1279-1281.

113. Mancini F, Zangaglia R, Cristina S, et al. Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in Parkinsonism. Mov Disord. 2003;18(6):685-688.

114. Ellies M, Rohrbach-Volland S, Arglebe C, et al. Successful management of drooling with botulinum toxin A in neurologically disabled children. Neuropediatrics. 2002;33(6):327-330.

115. Jongerius PH, Joosten F, Hoogen FJA, et al. The treatment of drooling by ultrasound-guided intraglandular injections of botulinum toxin type A into the salivary glands. Laryngoscope. 2003;113(1):107-111.

116. Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology. 2004;62(1):37-40.

117. De Seze M, Petit H, Gallien P, et al. Botulinum A toxin and detrusor sphincter dyssynergia: A double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol. 2002;42(1):56-62.

118. Dykstra DD, Sidi AA. Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: A double-blind study. Arch Phys Med Rehabil. 1990;71(1):24-26.

119. Schurch B, Hauri D, Rodic B, et al. Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: A prospective study in 24 spinal cord injury patients. J Urol. 1996;155(3):1023-1029.

120. Dykstra DD, Sidi AA, Scott AB, et al. Effects of botulinum A toxin on detrusor-sphincter dyssynergia in spinal cord injury patients. J Urol 1988;139(5):919-922.

121. Petit H, Wiart L, Gaujard E, et al. Botulinum A toxin treatment for detrusor-sphincter dyssynergia in spinal cord disease. Spinal Cord. 1998;36(2):91-94.

122. Kuo HC. Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. J Urol. 2003; 170(5):1908-1912.

123. Fowler CJ, Betts CD, Christmas TY, et al. Botulinum toxin in the treatment of chronic urinary retention in women. Br J Urol. 1992;70(4):387-389.

124. Porta M, Maggioni G, Ottaviani F, Shindler A. Treatment of phonic tics in patients with Tourette's syndrome using botulinum toxin type A. Neurol Sci. 2004;24(6):420-3.

125. Davies J, Duffy D, Boyt N, et al. Botulinum toxin (Botox) reduces pain after hemorrhoidectomy: Results of a double-blind, randomized study. Dis Colon Rectum. 2003;46(8):1097-1102.

126. Tan EK, Jankovic J. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. Neurology 1999;53(9):2102-7.

127. Relja M, Telarovic S. Botulinum toxin in tension-type headache. J Neurol 2004;251(Suppl 1): 112-114.

128. Rollnik JD, Dengler R. Botulinum toxin (Dysport) in tension-type headaches. Acta Neurochir Suppl. 2002;79:123-126.

129. Schulte-Mattler WJ, Krack P, BoNTTH Study Group. Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study. Pain. 2004;109(1-2):110-114.

130. Silva J, Pinto R, Carvalho T, et al. Intraprostatic Botulinum Toxin Type A injection in patients with benign prostatic enlargement: duration of the effect of a single treatment. BMC Urol. 2009;9:9.

131. Behmand RA, Tucker T, Guyuron B. Single-site botulinum toxin type a injection for elimination of migraine trigger points. Headache 2003;43(10):1085-1089.

132. Evers S, Vollmer-Haase J, Schwaag S et al. Botulinum toxin A in the prophylactic treatment of migraine-a randomized, double-blind, placebo-controlled study. Cephalalgia 2004;24(10): 838-43.

133. Mathew NT, Frishberg BM, et al. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double blind, placebo-controlled trial. Headache. 2005; 45(4):293-307.

134. Dodick DW, Mauskop A, et al. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache. 2005;45(4):315-24.

135. Silberstein SD, Stark SR, et al. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc.

2005;80(9):1126-37.

136. Eckardt A, Kuettner C. Treatment of gustatory sweating (Frey's syndrome) with botulinum toxin A. Head and Neck. 2003;25(8):624-8.

137. Kyrmizakis DE, Pangalos A et al. The use of botulinum toxin type A in the treatment of Frey and crocodile tears syndromes. J Oral Maxillofac Surg. 2004;62(7):840-4.

138. Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19):1707-14.

139. Hallan RI, Williams NS, Melling J, et al. Treatment of anismus in intractable constipation with botulinum A toxin. Lancet. 1988;2(8613):714-7.

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

141. Schurch B, de Seze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005;174(1):196-200.

142. Ghei M, Maraj BH, Miller R, et al. Effects of botulinum toxin B on refractory detrusor overactivity: a randomized, double-blind, placebo controlled, crossover trial. J Urol 2005;174(5):1873-7.

143. Giannantoni A, Di Stasi SM, Stephen RL, et al. Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study. J Urol 2004;172(1):240-3.

144. Cruz F, Herschorn S, Aliotta P, et al. Efficacy and Safety of OnabotulinumtoxinA in Patients with Urinary Incontinence Due to Neurogenic Detrusor Overactivity: A Randomised, Double-Blind, Placebo-Controlled Trial. Eur Urol (2011), doi:10.1016/ j.eururo.2011.07.002

145. Lacy BE, Crowell MD, Schettler-Duncan A, et al. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care. 2004;27(10):2341-7.

146. Apostolidis A, Dasgupta P, Denys P, et al. Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report. Eur Urol. 2009;55(1):100-20.

147. 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.

148. Oh TH, Brumfield KA, Hoskin TL, et al. Dysphagia in inclusion body myositis: clinical features, management, and clinical outcomes. Am J Phys Med Rehabil. 2008;87(11):883-9.

149. Krause E, Schirra J, Gurkov R. Botulinum toxin a treatment of cricopharyngeal dysphagia after subarachnoid hemorrhage. Dysphagia. 2008;23(4):406-10.

150. Suzukia Y, Sanio N, Shinonaga C, et al. Successful botulinum toxin treatment of dysphagia in a spinal muscular atrophy type 2 patient. Brain Dev. 2007;29(10):662-5.

151. Masiero S, Briani C, Marchese-Ragona R, et al. Successful treatment of long-standing post-stroke dysphagia with botulinum toxin and rehabilitation. J Rehabil Med. 2006;38(3):201-3.

152. Sewell RK, Bauman NM. Congenital cricopharyngeal achalasia: management with botulinum toxin before myotomy. Arch Otolaryngol Head Neck Surg. 2005;131(5):451-3.

153. Murry T, Wasserman T, Carrau RL, Castillo B. Injection of botulinum toxin A for the treatment of dysfunction of the upper esophageal sphincter. Am J Otolaryngol. 2005;26(3):157-62.

154. Marchese-Ragona R, Marioni G, Restivo DA, Staffieri A. Solving dysphagia due to cricopharyngeal muscle dysfunction with botulinum toxin. Eur Arch Otorhinolaryngol. 2005;262(3):250-1.

155. Liu LW, Tarnopoisky M, Armstrong D. Injection of botulinum toxin A to the upper esophageal sphincter for oropharyngeal dysphagia in two patients with inclusion body myositis. Can J Gastroenterol. 2004;18(6):397-9.

156. Chiu MJ, Chang YC, Hsiao TY. Prolonged effect of botulinum toxin injection in the treatment of cricopharyngeal dysphagia: case report and literature review. Dysphagia. 2004;19(1):52-7.

157. Alfonsi E, Merlo IM, Ponzio M, et al. An electrophysiological approach to the diagnosis of neurogenic dysphagia: implications for botulinum toxin treatment. J Neurol Neurosurg Psychiatry. 2010;81(1):54-60.

158. Parameswara MS, Soliman AM. Ann Otol Rhinol Laryngol. Endoscopic botulinum toxin injection for cricopharyngeal dysphagia. Ann Otol Rhinol Laryngol. 2002;111(10):871-4.

159. Restivo DA, Palmeri A, Marchese-Ragona R. Botulinum toxin for cricopharyngeal dysfunction in Parkinson's disease. N Eng J Med. 2002;346(15):1174-5.

160. Brant CQ, Siqueira ES, Ferrari AP Jr. Botulinum toxin for oropharyngeal dysphagia: case report of flexible endoscope-guided injection. Dis Esophagus. 1999;12(1):68-73.

161. Schneider I, Thumfart WF, Pototschnig C, Eckel HE. Treatment of dysfunction of the cricopharyngeal muscle with botulinum A toxin: introduction of a new, noninvasive method. Ann Otol Rhinol Laryngol. 1994;103(1):31-5.

162. Alberty J, Oelerich M, Ludwig K, et al. Efficacy of botulinum toxin A for treatment of upper esophageal sphincter dysfunction. Laryngoscope. 2000;110(7):1151-6.

163. Atkinson SI, Rees J. Botulinum toxin for cricopharyngeal dysphagia: case reports of CT-guided injection. J Otolaryngol. 1997;26(4):273-6.

164. Blitzer A, Brin MF. Use of botulinum toxin for diagnosis and management of cricopharyngeal achalasia. Otolaryngol Head Neck Surg. 1997;116(3):328-30.

165. Sampaio C, Ferreira JJ, Simoes F, et al. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. Mov Disord. 1997;12(6):1013-8.

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

167. Adler CH, Bansberg SF, Hentz JG, et al. Botulinum toxin type A for treating voice tremor. Arch Neurol. 2004;61(9):1416-20.

168. Saper JR, Mathew NT, Loder EW, et al. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type A injection sites and doses in the prevention of episodic migraine. Pain Med. 2007;8(6):478-85.

169. Elkind AH, O'Carroll P, Blumenfeld A, et al. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. J Pain. 2006;7(10):688-96.

170. Relja M, Poole AC, Schoenen J, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalgia. 2007;27(6):492-503.

171. Aurora SK, Gawel M, Brandes JL, et al. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache. 2007;47(4):486-99.

172. Helveston EM, Pogrebniak AE. Treatment of acquired nystagmus with botulinum A toxin. AM J Ophthalmol. 1988;106(5):584-6.

173. Leigh RJ, Tomsak RL, Grant MP, et al. Effectiveness of botulinum toxin administered to abolish acquired nystagmus. Ann Neurol. 1992;32(5):633-42.

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

175. Padberg M, de Bruijn SF, de Haan RJ, Tavy DL. Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial. Cephalalgia. 2004;24(8):675-80.

176. Porta M. Botulinum toxin type A injections for myofascial pain syndrome and tension-type headache. Eur J Neurol. 1999; 6:S103-109.

177. Zwart JA, Bovim G, Sand T, Sjaastad O. Tension headache: botulinum toxin paralysis of temporal muscles. Headache. 1994;34(8):458-62.

178. Kemal Erdemoglu A, Barlibas A. The long-term efficacy and safety of botulinum toxin in refractory chronic tension-type headache. J Headache Pain. 2007;8(5):294-300.

179. Ondo WG, Vuog KD, Derman HS. Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study. Cephalalgia. 2004;24(1):60-5.

180. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum Toxin Type A and Divalproex Sodium for Prophylactic Treatment of Episodic or Chronic Migraine. Headache. 2008;48(2):210-20.

181. Cady R. Schreiber C. Botulinum Toxin Type A as Migraine Preventive Treatment in Patients Previously Failing Oral Prophylactic Treatment Due to Compliance Issues. Headache.

2008;48(6):900-13.

182. Freitag FG, Diamon S, Diamond M, Urban G. Botulinum Toxin Type A in the Treatment of Chronic Migraine Without Medication Overuse. Headache. 2008;48(2):201-9.

183. Schwedt TJ, Hentz JG, Dodick DW. Factors associated with the prophylactic effect of placebo injections in subjects enrolled in a study of botulinum toxin for migraine. Cephalalgia. 2007;27(6):528-34.

184. Vo AH, Satori R, Jabbari B, et al. Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviat Space Environ Med. 2007;78(5 Suppl):B113-8.

185. Anand KS, Prasad A, Sing MM, et al. Botulinum toxin type A in prophylactic treatment of migraine. Am J Ther. 2006;13(3):183-7.

186. Eross EJ, Gladstone JP, Lewis S, et al. Duration of migraine is a predictor for response to botulinum toxin type A. Headache. 2005;45(4):308-14.

187. Conway S, Delplanche C, Crowder J, et al. Botox therapy for refractory chronic migraine. Headache. 2005;45(4):355-7.

188. Mathew NT, Kailasam J, Meadors L. Predictors of Response to Botulinum Toxin Type A (BoNTA) in Chronic Daily Headache. Headache. 2008;48(2);194-200.

189. Kwak CH, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol. 2000;57(8):1190-3.

190. Prabhakar A , Levine MS, Rubesin S,et al. Relationship between diffuse esophageal spasm and lower esophageal sphincter dysfunction on barium studies and manometry in 14 patients. AJR Am J Roentgenol. 2004;183(2):409-13.

191. Krause E, Hempel JM, Gürkov R. Botulinum toxin A prolongs functional durability of voice prostheses in laryngectomees with pharyngoesophageal spasm. Am J Otolaryngol. 2009 Nov-Dec;30(6):371-5.

192. de Bree R, Duyndam JE, Kuik DJ, Leemans CR. Repeated botulinum toxin type A injections to treat patients with Frey syndrome. Arch Otolaryngol Head Neck Surg. 2009;135(3):287-90.

193. Nava-Castaneda A, Tovilla-Canales JL, Boullosa V, et al. Duration of botulinum toxin effect in the treatment of crocodile tears. Ophthal Plast Reconstr Surg. 2006 Nov-Dec;22(6):453-6.

194. Kyrmizakis DE, Pangalos A, Papadakis CE, et al. The use of botulinum toxin type A in the treatment of Frey and crocodile tears syndromes. J Oral Maxillofac Surg. 2004 Jul;62(7):840-4.

195. Montoya FJ, Riddell CE, Caesar R, Hague S. Treatment of gustatory hyperlacrimation (crocodile tears) with injection of botulinum toxin into the lacrimal gland. Eye. 2002;16(6):705-9.

196. Simpson DM, Gracies JM, Graham HK, et al. Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review). Neurology. 2008;70(19):1691-8.

197. Fock J, Galea MP, Stillman BC, et al. Functional outcome following Botulinum toxin A injection to reduce spastic equinus in adults with traumatic brain injury. Brain Inj. 2004;18(1):57-63.

198. Pavesi G, Brianti R, Medici D, et al. Botulinum toxin type A in the treatment of upper limb spasticity among patients with traumatic brain injury. J Neurol Neurosurg Psychiatry. 1998;64(3):419-20.

199. Verplancke D, Snape S, Salisbury CF, et al. A randomized controlled trial of botulinum toxin on lower limb spasticity following acute acquired severe brain injury. Clin Rehabil. 2005;19(2):117-25.

200. Gorelick A, Barnett J, Chey W, Anderson M, Elta G. Botulinum toxin injection after biliary sphincterotomy. Endoscopy. 2004;36(2):170-3.

201. Banerjee B, Miedema B, Saifuddin T, Marshall JB. Intrasphincteric botulinum toxin type A for the diagnosis of sphincter of Oddi dysfunction: a case report. Surg Laparosc Endosc Percutan Tech. 1999;9(3):194-6.

202. Pasricha PJ, Miskovsky EP, Kalloo AN. Intrasphincteric injection of botulinum toxin for suspected sphincter of Oddi dysfunction. Gut. 1994 Sep;35(9):1319-21.

203. Wehrmann T, Schmitt TH, Arndt A, et al. Endoscopic injection of botulinum toxin in patients with recurrent acute pancreatitis due to pancreatic sphincter of Oddi dysfunction. Aliment Pharmacol Ther. 2000;14(11):1469-77.

204. Baldwin MK, Benumof JL. Paradoxical vocal cord movement: a unique case of occurrence and treatment. Anesthesiology. 2007;107(2):359.

205. 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.

206. El Maaytah M, Jerjes W, Upile T, et al. Bruxism secondary to brain injury treated with botulinum toxin-A: a case report. Head Face Med. 2006;2:41.

207. Santos MT, Manzano FS, Genovese WJ. Different approaches to dental management of self-inflicted oral trauma: oral shield, botulinum toxin type A neuromuscular block, and oral surgery. Quintessence Int. 2008;39(2):e63-9.

208. Monroy PG, da Fonseca MA. The use of botulinum toxin-a in the treatment of severe bruxism in a patient with autism: a case report. Spec Care Dentist. 2006;26(1):37-9.

209. Nash MC, Ferrell RB, Lombardo MA, et al. Treatment of bruxism in Huntington's disease with botulinum toxin. J Neuropsychiatry Clin Neurosci. 2004;16(3):381-2.

210. Tan EK, Chan LL, Chang HM. Severe bruxism following basal ganglia infarcts: insights into pathophysiology. J Neurol Sci. 2004;217(2):229-32.

211. See SJ, Tan EK. Severe amphetamine-induced bruxism: treatment with botulinum toxin. Acta Neurol Scand. 2003;107(2):161-3.

212. Ivanhoe CB, Lai JM, Francisco GE. Bruxism after brain injury: successful treatment with botulinum toxin-A. Arch Phys Med Rehabil. 1997;78(11):1272-3.

213. Kurtoglu C, Gur OH, Kurkcu M, et al. Effect of botulinum toxin-A in myofascial pain patients with or without functional disc displacement. J Oral Maxillofac Surg. 2008;66(8):1644-51.

214. Bakke M, Moller E, Werdelin LM, et al. Treatment of severe temporomandibular joint clicking

with botulinum toxin in the lateral pterygoid muscle in two cases of anterior disc displacement. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100(6):693-700.

215. Karacalar A, Yilmaz N, Bilgici A, et al. Botulinum toxin for the treatment of temporomandibular joint disk disfigurement: clinical experience. J Craniofac Surg. 2005;16(3):476-81.

216. Aquilina P, Vickers R, McKellar G. Reduction of a chronic bilateral temporomandibular joint dislocation with intermaxillary fixation and botulinum toxin A. Br J Oral Maxillofac Surg. 2004;42(3):272-3.

217. Martinez-Perez D, Garcia Ruiz-Espiga P. Recurrent temporomandibular joint dislocation treated with botulinum toxin: report of 3 cases. J Oral Maxillofac Surg. 2004;62(2):244-6.

218. Borodic GE, Acquadro MA. The use of botulinum toxin for the treatment of chronic facial pain. J Pain. 2002;3(1):21-7.

219. Feund BJ, Schwartz M. Intramuscular injection of botulinum toxin as an adjunct to arthrocentesis of the temporomandibular joint: preliminary observations. Br J Oral Maxillofac Surg. 2003;41(5):351-2.

220. Ziegler CM, Haag C, Muhling J. Treatment of recurrent temporomandibular joint dislocation with intramuscular botulinum toxin injection. Clin Oral Investig. 2003;7(1):52-5.

221. Freund BJ, Schwartz M. Relief of tension-type headache symptoms in subjects with temporomandibular disorders treated with botulinum toxin-A. Headache. 2002;42(10):1033-7.

222. von Lindern JJ. Type A botulinum toxin in the treatment of chronic facial pain associated with temporo-mandibular dysfunction. Acta Neurol Belg. 2001;101(1):39-41.

223. Freund B, Schwartz M, Symington JM. The use of botulinum toxin for the treatment of temporomandibular disorders: preliminary findings. J Oral Maxillofac Surg. 1999;57(8):916-20.

224. Daelen B, Thorwirth V, Koch A. Treatment of recurrent dislocation of the temporomandibular joint with type A botulinum toxin. Int J Oral Maxillofac Surg. 1997;26(6):458-60.

225. Vázquez Bouso O, Forteza González G, Mommsen J, et al. Neurogenic temporomandibular joint dislocation treated with botulinum toxin: report of 4 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(3):e33-7.

226. Lew HL, Lee EH, Castaneda A, et al. Therapeutic use of botulinum toxin type A in treating neck and upper-back pain of myofascial origin: a pilot study. Arch Phys Med Rehabil. 2008;89(1):75-80.

227. Qerama E, Fuglsang-Frederisksen A, Kasch H, et al. A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. Neurology. 2006;67(2):241-5.

228. Gobel H, Heinze A, Reichel G, et al. Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study. Pain. 2006;125(1-2):82-8.

229. Ojala T, Arokoski JP, Partanen J. The effect of small doses of botulinum toxin a on neck-shoulder myofascial pain syndrome: a double-blind, randomized, and controlled crossover trial. Clin J Pain. 2006;22(1):90-6.

230. Graboski CL, Gray DS, Burnham RS. Botulinum toxin A versus bupivacaine trigger point injections for the treatment of myofascial pain syndrome: a randomized double blind crossover study. Pain. 2005;118(1-2):170-5.

231. Ferrante FM, Bearn L, Rothrock R, King L. Evidence against trigger point injection technique for the treatment of cervicothoracic myofascial pain with botulinum toxin type A. Anesthesiology. 2005;102(2):377-83.

232. Kamanli A, Kaya A, Ardicoglu O, et al. Comparison of lidocaine injection, botulinum toxin injection, and dry needling to trigger points in myofascial pain syndrome. Rheumatol Int. 2005;25(8):604-11.

233. Lang AM. A preliminary comparison of the efficacy and tolerability of botulinum toxin serotypes A and B in the treatment of myofascial pain syndrome: a retrospective, open-label chart review. Clin Ther. 2003;25(8):2268-78.

234. De Andres J, Cerda-Olmedo G, Valia JC, et al. Use of botulinum toxin in the treatment of chronic myofascial pain. Clin J Pain. 2003;19(4):269-75.

235. Wheeler AH, Goolkasian P, Gretz SS. A randomized, double-blind, prospective pilot study of botulinum toxin injection for refractory, unilateral, cervicothoracic, paraspinal, myofascial pain syndrome. Spine. 1998;23(15):1662-6.

236. Cheschire WP, Abaschian SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. Pain. 1994;59(1):65-9.

237. Basciani M, Intiso D. Botulinum toxin type-A and plaster cast treatment in children with upper brachial plexus palsy. Pediatr Rehabil. 2006;9(2):165-70.

238. Price AE, Ditaranto P, Yaylali I, et al. Botulinum toxin type A as an adjunct to the surgical treatment of the medial rotation deformity o the shoulder in birth injuries of the brachial plexus. J Bone Joint Surg Br. 2007;89(3):327-9.

239. Wutthiphan S. Role of botulinum toxin A in diplopia following orbital decompression. Strabismus. 2008;16(3):112-5.

240. Ebner R. Botulinum toxin type A in upper lid retraction of Graves' ophthalmopathy. J Clin Neuroophthalmol. 1993;13(4):258-61

241. Korn BS, Seo SW, Levi, L, et al. Optic neuropathy associated with botulinum A toxin in thyroid-related orbitopathy. Ophthal Plast Reconstr Surg. 2007;23(2):109-14.

242. Siglmayer N, Lesin M, Juri J, et al. Treatment of ocular motility disturbances in Graves' disease with botulinum toxin A. Coll Antropol. 2005;29 Suppl 1:41-6.

243. Fu KY, Chen HM, Sun ZP, et al. Long-term efficacy of botulinum toxin type A for the treatment of habitual dislocation of the temporomandibular joint. Br J Oral Maxillofac Surg. 2009 Aug 6. [Epub ahead of print]

244.. Yoon SJ, Ho J, Kang HY, et al. Low-dose botulinum toxin type A for the treatment of refractory piriformis syndrome. Pharmacotherapy. 2007;27(5):657-65.

245. Restivo DA, Lanza S, Marchese-Ragona R, et al. Improvement of masseter spasticity by

botulinum toxin facilitates PEG placement in amyotrophic lateral sclerosis. Gastroenterology. 2002;123(5):1749-50.

246. 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(5):704-7.

247. Sapci T, Yazici S, Evcimik MF, et al. Investigation of the effects of intranasal botulinum toxin type A and ipratropium bromide nasal spray on nasal hypersecretion in idiopathic rhinitis without eosinophilia. Rhinology. 2008;46(1);45-51.

248. Oskarsson E, Piehl AK, Gustafsson BE, Pettersson K. Improved intramuscular blood flow and normalized metabolism in lateral epicondylitis after botulinum toxin treatment. Scan J Med Sci Sports. Scand J Med Sci Sports. 2009;19(3):323-8.

249. Placzek R, Drescher W, Deuretzbacher G, et al. Treatment of chronic radial epicondylitis with botulinum toxin A. A double-blind, placebo-controlled, randomized multicenter study. J Bone Joint Surg Am. 2007;89(2):255-60.

250. Wong SM, Hui AC, Tong PY, et al. Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2005;143(11):793-7.

251. Hayton MJ, Santini AJ, Hughes PJ, et al. Botulinum toxin injection in the treatment of tennis elbow. A double-blind, randomized, controlled pilot study. J Bone Joint Surg Am. 2005;87(3):503-7.

252. Akbar M, Abel, R, Seyler-Thorsten M, et al. Repeated botulinum-A toxin injections in the treatment of myelodysplastic children and patients with spinal cord injuries with neurogenic bladder dysfunction. BJU Int. 2007;100(3):639-45.

253. Grosse J, Kramer G, Stöhrer M. Success of repeat injections of botulinum A toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol. 2005;47(5):653-9.

254. Liguori R, Cordivari C, Lugaresi E, Montagna P. Botulinum toxin A improves muscle spasms and rigidity in stiff-person syndrome. Mov Disord. 1997;12(6):1060-3.

255. Patki PS, Hamid R, Arumugam K, et al. Botulinum toxin-type A in the treatment of drug-resistant neurogenic detrusor overactivity secondary to traumatic spinal cord injury. BJU Int. 2006;98(1):77-82.

256. Hung HL, Kao LY, Sun MH. Botulinum toxin treatment for acute traumatic complete sixth nerve palsy. Eye. 2005;19(3):337-41.

257. Holmes JM, Leske DA, Christiansen SP. Initial treatment outcomes in chronic sixth nerve palsy. J AAPOS. 2001;5(6):370-6.

258. Chuenkongkaew W, Dulayajinda D, Deetae R. Botulinum toxin treatment of the sixth nerve palsy: an experience of 5-year duration in Thailand. J Med Assoc Thai. 2001;84(2):171-6.

259. Holmes JM, Beck RW, Kip KE, et al. Botulinum toxin treatment versus conservative management in acute traumatic sixth nerve palsy or paresis. J AAPOS. 2000;4(3):145-9.

260. Del Popolo G, Filocamo MT, Li Marzi V, et al. Neurogenic Detrusor Overactivity Treated with English Botulinum Toxin A: 8-Year Experience of One Single Centre. Eur Urol. 2008;53(5):1013-20.

261. Aguirregomozcorta M, Pagonabarraga J, Diza-Manera J, et al. Efficacy of botulinum toxin in severe Tourette syndrome with dystonic tics involving the neck. 2008;14(5):443-5.

262. Trimble MR, Whurr R, Brookes G, Robertson MM. Vocal tics in Gilles de la Tourette syndrome treated with botulinum toxin injections. Mov Disord. 1998;13(3):617-9.

263. Jankovic J. Botulinum toxin in the treatment of dystonic tics. Mov Disord. 1994;9(3):347-9.

264. Salloway S, Stewart CF, Israeli L, et al. Botulinum toxin for refractory vocal tics. Mov Disord. 1996;11(6):746-8.

265. Patti R, Almasio PL, Arcara M, eta l. Botulinum toxin vs. topical glyceryl trinitrate ointment for pain control in patients undergoing hemorrhoidectomy: a randomized trial. Dis Colon Rectum. 2006;49(11):1741-8.

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

267. Lagalla G, Millevolte M, Capecci M, et al. Long-lasting benefits of botulinum toxin type B in Parkinson's disease-related drooling. J Neurol. 2009;256(4):563-7.

268. Wilken B, Aslami B, Backes H. Successful treatment of drooling in children with neurological disorders with botulinum toxin A or B. Neuropediatrics. 2008;39(4):200-4.

269. Racette BA, Good L, Sagitto S, Perimutter JS. Botulinum toxin B reduces sialorrhea in parkinsonism. Mov Disord. 2003;18(9):1059-61.

270. Coleski R, Anderson MA, Hasler WL. Factors Associated with Symptom Response to Pyloric Injection of Botulinum Toxin in a Large Series of Gastroparesis Patients. Dig Dis Sci. 2009 Jan 30. [Epub ahead of print]

271. Reddymasu SC, Singh S, Sankula R, et al. Endoscopic pyloric injection of botulinum toxin-A for the treatment of postvagotomy gastroparesis. Am J Med Sci. 2009;337(3):161-4.

272. Mirbaheri SA, Sadeghi A, Amouie M, et al. Pyloric injection of botulinum toxin for the treatment of refractory GERD accompanied with gastroparesis: a preliminary report. Dig Dis Sci. 2008;53(10):2621-6.

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

274. 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;26(9):1251-8.

275. Arts J, van Gool S, Caenepeel P, et al. Influence of intrapyloric botulinum toxin injection on gastric emptying and meal-related symptoms in gastroparesis patients. Aliment Pharmacol Ther. 2006;24(4):661-7.

276. Ben-Youssef R, Baron PW, Franco E, et al. Intrapyloric injection of botulinum toxin a for the treatment of persistent gastroparesis following successful pancreas transplantation. Am J Transplant. 2006;6(1):214-8.

277. Bromer MQ, Friedenberg F, Miller LS, et al. Endoscopic pyloric injection of botulinum toxin A for the treatment of refractory gastroparesis. Gastrointest Endosc. 2005;61(7):833-9.

278. Ehren I, Volz D, Farrelly E, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: A randomized, placebo-controlled, double-blind study. Scand J Urol Nephrol. 2007;41(4):335-40.

279. Schurch B, Stöhrer M, Kramer G, et al. Botulinum toxin-A to treat detrusor hyperreflexia in spinal cord injured patients. Neurourol Urodyn. 2001;20(Abstract 92):521-2.

280. Ruffion A, Capelle O, Paparel P, et al. What is the optimum dose of type A botulinum toxin for treating neurogenic bladder overactivity? BJU Int. 2006;97(5):1030-4.

281. Shuhendler AJ, Lee S, Se B, et al. Efficacy of Botulinum Toxin Type A for the Prophylaxis of Episodic Migraine Headaches: A Meta-analysis of Randomized, Double-Blind, Placebo-Controlled Trials. Pharmacotherapy. 2009;29(7):784-91.

282. Kanovsky P, Slawek J, Denes Z, et al. Efficacy and Safety of Botulinum Neurotoxin NT 201 in Poststroke Upper Limb Spasticity. Clin Neuropharm 2009;32:259-265.

283. Barnes M, Schnitzler A, Medeiros L, et al. Efficacy and safety of NT 201 for upper limb spasticity of various etiologies – a randomized parallel-group study. Acta Neurol Scand 2010;122:295–302.

284. Rohrbach S, Junghans K, Köhler S, Laskawi R. Minimally invasive application of botulinum toxin A in patients with idiopathic rhinitis. Head Face Med. 2009;16;5:18.

285. Kuo HC, Liu HT. Therapeutic effects of add-on botulinum toxin A on patients with large benign prostatic hyperplasia and unsatisfactory response to combined medical therapy. Scand J Urol Nephrol. 2009;43(3):206-11.

286. Editor's Note to Authors and Readers: Levels of Evidence coming to *Neurology*®. Accessed June 21, 2010 at http://www.neurology.org/misc/NeurologyFiller.pdf.

287. Snow V, Weiss K, Wall EM, Mottur-Pilson C, for the American Academy of Family Physicians and the American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. Ann Intern Med. 2002;137:840-849.

288. Xeomin [prescribing information]. Greensboro, NC: Merz Pharmaceuticals, LLC, April 2014.

289. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012; 78:1337-1345.

290. Hayes medical Technology Directory. Trigger Point Injections for Myofacial Pain. December 24, 2013. Available at https://www.hayesinc.com. Accessed on May 15, 2014.

291. 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.

292. Jarvis SK, Abbott JA, Lenart MS, et al. Pilot study of botulinum toxin type A in the treatment of chronic pelvic pain associated with spasm of the levator ani muscles. Aust N Z J Obstet Gynaecol 2004;44:46–50.

293. Bohluli B, Motamedi MH, Bagheri SC, et al. Use of botulinum toxin A for drug-refractory trigeminal neuralgia: preliminary report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 Jan;111(1):47-50. Epub 2010 Jul 31.

294. Zuniga C, Diaz S, Piedimonte F, et al. Beneficial effects of botulinum type A in trigeminal neuralgia. Arq Neuropsiquiatr. 2008 Sep;66(3A):500-3.

295. Piovesan EJ, Teive HG, Kowacs PA, et al. An open study of botulinum-A toxin treatment of trigeminal neuralgia. Neurology. 2005 Oct 25;65(8):1306-8.

296. Hayes Medical Technology Directory. Botulinum Toxin Treatment for Migraine Headache. September 22, 2011. Available at https://www.hayesinc.com. Accessed on May 15, 2014.

297. Dressler D. Routine use of Xeomin in patients previously treated with Botox: long term results. European Journal of Neurology. 2009;16(Suppl 2):2-5.

298. Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, Furlan AD. 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.

299. Hayes Medical Technology Directory. Botulinum Toxin Treatment for Chronic Tension-Type Headache. December 30, 2011. Available at https://www.hayesinc.com. Accessed on May 15, 2014.

300. Ramadan NM, Silberstein SD, Freitag FG, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. 2000. Available at: http://www.aan.com/professionals/practice/pdfs/gl0090.pdf. Accessed May 10, 2013.

301. Bjornson K, Hays R, Graubert C, et al. Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. Pediatrics. 2007 Jul;120(1):49-58.

302. MCG Milliman Care Guidelines®. Ambulatory Care 18th Edition. OnabotulinumtoxinA. Available at http://careweb.careguidelines.com/ed18/index.html. Accessed on May 15, 2014.

303. MCG Milliman Care Guidelines®. Ambulatory Care 18th Edition. AbobotulinumtoxinA. Available at http://careweb.careguidelines.com/ed18/index.html. Accessed on May 15, 2014.

304. MCG Milliman Care Guidelines®. Ambulatory Care 18th Edition. RimabotulinumtoxinB. Available at http://careweb.careguidelines.com/ed18/index.html. Accessed on May 15, 2014.

305. Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. Eur J Neurol. 2011 Jan;18(1):5-18. doi: 10.1111/j.1468-1331.2010.03042.x.

306. Novak I, Campbell L, Boyce M, et al. Botulinum toxin assessment, intervention and aftercare for cervical dystonia and other causes of hypertonia of the neck: international consensus statement.Eur J Neurol. 2010 Aug;17 Suppl 2:94-108. doi: 10.1111/j.1468-1331.2010.03130.x.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
9/1/2014	Policy revised per annual review. Added general instructions for medical necessity review. Revised medical necessity criteria for the treatment of cervical dystonia to include symptoms of pain and/or functional impairment. Revised onabotulinumtoxinA criteria for the prevention of migraine headaches. Updated clinical evidence and references. Updated list of ICD-9 codes (added 378.82) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 7/8/2014. Policy 2014D0017M archived.
2/1/2014	Policy revised. Removed Xeomin dosing criterion for cervical dystonia. Approved by the National Pharmacy & Therapeutics Committee on 12/13/2013. Policy 2013D0017L archived.
10/1/2013	Policy revised per annual review. Coverage Rationale reformatted to list each botulinum toxin individually. Added OAB to the list of proven indications for onabotulinumtoxinA. Revised medical necessity criteria for migraine prophylaxis. Added medical necessity criteria for cervical dystonia, chronic anal fissure, detrusor overactivity and detrusor sphincter dyssynergia due to spinal cord injury or disease. Updated FDA section to include new indication for onabotulinumtoxinA (treatment of overactive bladder). Updated list of ICD-9 codes (added 596.51, 788.31, 788.33, and 951.4; removed 781.7) and associated ICD-10 codes. Approved by the National Pharmacy & Therapeutics Committee on 7/9/2013. Policy 2012D0017K archived.
9/1/2012	Policy revised per annual review. Clinical evidence and references updated. Added Cochrane review on low back pain. Added Hayes Medical Technology Directory on tension-type headache. Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/14. Approved by the National Pharmacy & Therapeutics Committee on 7/10/2012. Policy 2012D0017J archived.
1/1/2012	Policy revised. Removed detrusor-sphincter dyssynergia due to multiple sclerosis from the list of unproven uses for botulinum toxin type A. Added Hayes Medical Technology Directory on migraine headache. Updated FDA section to include new indication for onabotulinumtoxinA (treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition). Replaced code Q2040 with code J0588, which becomes effective on 1/1/2012. Approved by the National Pharmacy & Therapeutics Committee on 11/8/2011. Policy 2011D0017I archived.
9/1/2011	Policy revised per annual review. Added trigeminal neuralgia to the list of unproven uses. Added Hayes Technology Directory on gastroparesis. Updated list of proven ICD-9 codes (added 351.9 and 724.3; removed 333.1, 340, and 350.1). Clinical Evidence and References updated. Approved by the National Pharmacy & Therapeutics Committee on 7/12/2011. Policy 2010D0017H archived.
3/25/2011	Policy updated with addition of code Q2040, which becomes effective on 4/1/2011.
11/17/2010	Policy revised. Added Xeomin (incobotulinumtoxinA). Changed migraine headache to proven status for onabotulinumtoxinA. Added ICD-9 codes 333.1, 344.61, 346.70, 346.71, 346.72, 346.73, 351.1, 355.0, and 784.40. Approved by the National Pharmacy & Therapeutics Committee on 11/17/2010. Policy 2010D0017G archived.
8/16/2010	Policy revised per annual review. Added spasticity associated with spinal cord injury as proven for botulinum toxin type A. Added ICD-9 codes 333.89, 343.3, 343.4, and 343.9. Approved by the National Pharmacy & Therapeutics

	Committee on 5/11/2010. Policy revised to change spasticity associated with traumatic brain injury or spinal cord injury to spasticity associated with other injury, disease, or tumor of the brain or spinal cord. Added Professional Societies section. Approved by the National Pharmacy & Therapeutics Committee on 8/11/2010. Policy 2009D0017F archived.
11/16/2009	Policy revised with changes to Coverage Rationale: spasticity associated with traumatic brain injury and neurogenic detrusor hyperreflexia added as proven for botulinum toxin type A; sialorrhea and neurogenic detrusor hyperreflexia added as proven for botulium toxin type B; specified that botulinum toxin type A is proven for detrusor-sphincter dyssynergia due to spinal cord injury or disease, but unproven for detrusor-sphincter dyssynergia due to multiple sclerosis. Added ICD-9 codes 784.42 and 596.54 and removed 784.49. Added Dysport to the policy. Approved by National Pharmacy & Therapeutics Committee on 6/9/2009. Policy 2008D0017E archived.
9/10/2008	Policy revised with changes in the coverage rationale. Approved by National Pharmacy & Therapeutics Committee on 6/10/2008. Policy 20070017D archived.
3/12/2008	ICD 9 Codes added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.
1/11/2007	Policy revised with changes in the coverage rationale. Approved by National Pharmacy & Therapeutics Committee on 1/9/2007. Policy 2006D0017C archived.
9/14/2006	Policy revised with changes in coverage rationale. Approved by National Pharmacy & Therapeutics Committee on 9/12/2006. Policy 2004D0017B archived.
10/21/2005	HCPCS codes added to Coding Section per direction from the Reimbursement Medical Policy Operations Manager.
8/2/2005	Policy updated. Policy 2003D0017A archived.
6/20/2003	Approved by National Pharmacy & Therapeutics Committee on 6/10/2003. Policy 2002D0017A archived.
6/11/2002	Policy updated. Policy 2001D0017B archived.
3/10/2002	Policy updated. Policy 2001D0017A archived.
6/15/2001	New policy 2001D0017A. Approved by National Pharmacy & Therapeutics Committee on 6/12/2001.