

# The Regence Group

**Regence BlueCross BlueShield of Oregon · Regence BlueShield  
Regence BlueCross BlueShield of Utah · Regence BlueShield of Idaho  
Independent licensees of the Blue Cross and Blue Shield Association**

**Medication Policy Manual**

**Policy No:** dru006

**Topic:** Botox<sup>®</sup>, botulinum toxin type A injection

**Date of Origin:** January 1996

**Revised/Effective Date:** April 7, 2009

**Next Review Date:** March 2010

## **IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

## **Description**

Botulinum toxin is a neurotoxin that is injected into a muscle to cause temporary paralysis of that muscle.

## Policy / Criteria

- I.** Most contracts require prior authorization approval of botulinum toxin type A prior to coverage. Botulinum toxin type A may be considered medically necessary in patients with functional impairment originating from spasticity or dystonia (conditions of involuntary sustained muscle contraction) resulting from one of the following conditions:
- A.** Blepharospasm <sup>[1-3]</sup>
  - B.** Central demyelinating of corpus callosum <sup>[2]</sup>
  - C.** Cerebral Palsy <sup>[2,15]</sup>
  - D.** Cervical dystonia <sup>[1-4]</sup> with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures
  - E.** Demyelinating diseases of CNS <sup>[2]</sup>
  - F.** Facial nerve VII disorders <sup>[1-3]</sup>
  - G.** Facial nerve disorders, other <sup>[1,2,15]</sup>
    - facial myokymia, Melkersson's syndrome, facial/hemifacial spasms
  - H.** Hereditary spastic paraplegia <sup>[2,15]</sup>
  - I.** Laryngeal spasm; laryngeal adductor spastic dysphonia, or stridulus <sup>[2]</sup>
  - J.** Leukodystrophy (CNS disease characterized by adrenal atrophy and diffuse cerebral demyelination) <sup>[2]</sup>
  - K.** Multiple sclerosis <sup>[4,8,15]</sup>
  - L.** Neuromyelitis optica <sup>[2,3]</sup>
  - M.** Organic writer's cramp <sup>[2,15]</sup>
  - N.** Orofacial dyskinesia (i.e., jaw closure dystonia) <sup>[2,15]</sup>
  - O.** Schilder's disease <sup>[2]</sup>
  - P.** Sialorrhea (drooling) in patients with Parkinson's Disease <sup>[40-42,57]</sup>
  - Q.** Spasmodic dysphonia <sup>[1,2,15]</sup>
  - R.** Spasmodic torticollis or unspecified torticollis <sup>[2]</sup> with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures
  - S.** Spastic hemiplegia <sup>[2,15,35]</sup>
    - spasticity related to stroke <sup>[5-7,15,35]</sup>

- spasticity related to spinal cord injury <sup>[15]</sup>

**T.** Strabismus <sup>[1-3]</sup>

**U.** Torsion dystonia, idiopathic and symptomatic (also known as Oppenheim's dystonia) <sup>[2,15]</sup>

**II.** Botulinum toxin type A may be considered medically necessary in patients with functional impairment resulting from one of the following conditions when generally accepted treatments are not effective or not tolerated:

**A.** Anal fissures <sup>[2]</sup> - patients will be assessed for trial and/or failure with other therapeutic alternatives, such as nitroglycerin ointment.

**B.** Achalasia/Cardiospasm <sup>[2]</sup> - in patients who have not responded to dilation therapy or who are considered poor surgical candidates.

**C.** Hyperhidrosis <sup>[11]</sup> - treatable primary medical conditions causing secondary hyperhidrosis should be identified and addressed where possible. Treatment of hyperhidrosis, including gustatory hyperhidrosis, may be considered medically necessary only when the hyperhidrosis is persistent and severe, and has resulted in significant medical complications such as skin maceration with secondary infection. Medical treatment of persistent hyperhidrosis is considered not medically necessary in the absence of significant medical complications associated with the condition.

**D.** Incontinence due to detrusor overactivity, either idiopathic or due to neurogenic causes (e.g., spinal cord injury, multiple sclerosis) when therapy with anticholinergic agents is not effective or not tolerated. <sup>[2,37-39, 48]</sup>

**III.** Administration, Quantity Limitations, and Authorization Period

**A.** Regence does not consider botulinum toxin type A to be a self-administered medication.

**B.** For conditions defined in Section I: When prior authorization is approved, botulinum toxin type A may be authorized in quantities up to 4 injection treatments within a 12 month period. Additional treatments may be authorized on a case by case basis if documentation of objective measures supporting the need for more frequent dosing are provided.

- C.** For conditions defined in Section II: When prior authorization is approved, botulinum toxin type A may be initially authorized in quantities up to 2 injection treatments within a 6 month period. Documentation of objective clinical response is necessary for continued authorization. After the initial authorization, up to 4 injection treatments over a 12 month period may be considered medically necessary if objective measures support clinical benefits from treatment.
  
- IV.** Botulinum toxin type A is considered not medically necessary for skin wrinkles <sup>[2, 14]</sup> or other cosmetic indications.
  
- V.** Botulinum toxin type A is considered investigational for all other indications, including, but not limited to:

  - A.** Allergic rhinitis <sup>[45]</sup>
  - B.** Benign prostatic hyperplasia <sup>[58]</sup>
  - C.** Chronic daily headache <sup>[2,54-55]</sup>
  - D.** Chronic motor tic disorder <sup>[2]</sup>
  - E.** Dermatochalasis <sup>[61]</sup>
  - F.** Diabetic and idiopathic gastroparesis <sup>[52,69]</sup>
  - G.** Interstitial cystitis <sup>[2,73]</sup>
  - H.** Low back pain <sup>[2,13,33]</sup>
  - I.** Migraine headaches <sup>[28,29,56, 76, 77]</sup>
  - J.** Myofascial pain <sup>[59,60]</sup>
  - K.** Piriformis syndrome (entrapment of the sciatic nerve by the piriformis muscle)
  - L.** Obesity <sup>[53,62]</sup>
  - M.** Pelvic floor spasm <sup>[63]</sup>
  - N.** Plantar fasciitis pain <sup>[50]</sup>
  - O.** Temporomandibular dysfunction (TMJ) <sup>[88-91]</sup>
  - P.** Tennis elbow (lateral epicondylitis) <sup>[51]</sup>

- Q. Tension headaches [2,12,42-44]
- R. Tics associated with Tourette syndrome [2]
- S. Tremors such as essential (benign) tremor
- T. Voice tremor [46]
- U. Thoracic outlet syndrome [79]

### **Position Statement**

- Conditions for which use of botulinum toxin type A (BTX-A) may be considered medically necessary are based on evidence supported by randomized controlled trials. [3]
- Botulinum toxins (BTX-A and BTX-B) are also being investigated in many different conditions where muscle tension is thought to play a role. The quality of evidence from the majority of these studies is poor because they lack controls, are not randomized or blinded, and only involve small numbers of subjects.
- All literature reviewed for this policy applies to treatment with BTX-A only and cannot be extrapolated to the use of other botulinum toxin serotypes.
- Use of botulinum toxin (all serotypes) for treatment of wrinkles or other cosmetic conditions is considered not medically necessary.

### ***Level of evidence in various conditions***

#### *Achalasia*

- Pneumatic dilation is the preferred medical treatment option for achalasia.
- One comparative trial demonstrated that pneumatic dilation produces a higher remission rate at 12 months (70%) compared to a 32% remission rate for BTX-A. [19]

#### *Allergic Rhinitis*

- One small (n=34) randomized controlled trial of 8 week duration suggests efficacy of BTX-A in relieving rhinorrhea, nasal obstruction and sneezing due to allergic rhinitis. There was no difference between BTX-A and placebo groups for the symptom of itching. [45]
- Well-designed, large-scale trials with repeated injections and comparison to nasal steroids are necessary to validate positive benefits of using BTX-A in this condition.

### *Anal Fissures*

- Both nitroglycerin ointment and BTX-A have been studied in the treatment of anal fissures.
  - \* Of the two treatments, nitroglycerin ointment is the least invasive.
  - \* Several small studies suggest healing rates of up to 70% with BTX-A. [16-17, 47]
  - \* Trials comparing nitroglycerin ointment with BTX-A show inconsistent results.
    - \*\* A comparative trial demonstrated a healing rate of 52% with nitroglycerin compared to 24% with BTX-A after 2 weeks of treatment. [64]
    - \*\* A second comparative trial demonstrated a healing rate of 60% with nitroglycerin ointment compared to 96% with BTX-A. [18]

### *Benign Prostatic Hyperplasia (BPH)*

- A small, poor quality trial comparing the effects of BTX-A with or without an alpha-adrenergic antagonist suggest possible BTX-A efficacy. The absence of a placebo comparator makes it difficult to determine the true efficacy of BTX-A. [58] Additional well-controlled studies are needed before BTX-A can be considered safe and effective in this condition.

### *Cervical dystonia (spasmodic torticollis)*

- Cervical dystonia (or spasmodic torticollis) is characterized by involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures. [80]
- Clinical trials evaluating the efficacy of botulinum toxin type A in cervical dystonia demonstrated a significant decrease in the cervical dystonia severity scale (CDSS) along with an improved physicians global assessment score 6 weeks after injection relative to placebo. The CDSS is an objective measurement used to quantify the severity of abnormal head positioning that results from cervical dystonia.
- In another trial, botulinum toxin type A improved head position by approximately 5 to 11 degrees for up to 8 weeks when compared with placebo. [92]

### *Dermatochalasis*

- Dermatochalasis is a condition in which a fold of skin develops in the eyelid, potentially leading to impaired vision, blepharitis, and dermatitis. Surgery is the current standard of care.

- A small, poor quality study (open-label study without a placebo comparator) suggests that BTX-A may be an effective treatment for upper eyelid dermatochalasis. <sup>[61]</sup> Additional well-controlled studies are needed before BTX-A can be considered safe and effective in this condition.

### *Gastroparesis (diabetic and idiopathic)*

- Several small, poor quality trials studied BTX-A in the treatment of gastroparesis. Improvement in gastric emptying time was inconsistent with some trials showing possible benefit <sup>[52, 69]</sup> and others showing no benefit <sup>[81, 82]</sup>. Additional well-controlled studies are needed before BTX-A can be considered safe and effective in this condition.

### *Headache*

- Chronic Daily Headache (CDH): BTX-A has not been shown to be effective in treatment or prevention of CDH. <sup>[54, 55, 83]</sup>
- Migraine Headache
  - \* Evidence supporting the efficacy of BTX-A in the treatment of migraines has always been equivocal, but the cumulative results of large randomized controlled trials now indicate the Botox is not an effective treatment option for migraines.
  - \* Collective results of seven randomized, controlled episodic migraine trials (totaling more than 1000 patients) have failed to demonstrate a significant difference between BTX-A and placebo in migraine prevention. Pre-specified primary endpoints and most secondary endpoints were not met. <sup>[29, 56, 65, 76,77]</sup>
  - \* There is no evidence that directly compares BTX-A with other prophylactic therapies such as calcium channel blockers, beta-blockers, or non-steroidal anti-inflammatory drugs. <sup>[2]</sup>
- Tension Headache
  - \* Current evidence is insufficient to permit conclusions regarding BTX-A as prophylactic therapy in patients with chronic tension headaches refractory to pharmacologic therapy. <sup>[27-29,36,42-44]</sup>
    - The majority of trials using BTX-A do not support its efficacy in the treatment of tension headaches. <sup>[27,42,44,84]</sup>
- The American Academy of Neurology (AAN) does not support the use of BTX-A in the prevention or treatment of headaches. <sup>[85]</sup> The AAN Technology Assessment of botulinum toxin concludes that:

- \* BTX-A is likely ineffective in treatment of episodic migraine and chronic tension-type headache.
- \* There is no consistent or strong evidence that BTX-A is effective in the treatment of chronic daily headache.

### *Hyperhidrosis*

- There are several double-blind trials that evaluate BTX-A in patients with primary axillary and primary palmar hyperhidrosis. <sup>[3,21, 74]</sup>
  - \* Treated palms with BTX-A were associated with a 26% reduction in sweating (measured by ninhydrin sweat testing) compared to no reduction with placebo. <sup>[21]</sup>
  - \* In two pivotal trials, 81% to 91% of patients treated for primary axillary hyperhidrosis achieved a greater than 50% reduction in axillary sweating at 4 weeks compared with 36% to 41% in the placebo group. <sup>[3]</sup>
- The median duration of effect in two pivotal trials that evaluated BTX-A in primary axillary hyperhidrosis was 201 days. <sup>[3]</sup>
- Reduction in sweating is also described in case series reports for both palmar and axillary hyperhidrosis with BTX-A injections lasting up to 5-12 months. <sup>[22-23]</sup>
- However, despite the reduction in sweating, BTX-A does not affect the unpleasant odor.
- In a small case study, intracutaneous BTX-A was effective in ceasing gustatory sweating up to a mean duration of 17 months. <sup>[20]</sup>

### *Interstitial Cystitis*

- Four, poor quality studies (case series) have assessed BTX-A treatment for pain and improvement of bladder capacity in patients with interstitial cystitis. All reports suggest efficacy, though results have not been confirmed in larger controlled trials. <sup>[2, 73]</sup>

### *Low Back Pain*

- Several small, poor quality trials evaluate BTX-A in the treatment of low back pain. <sup>[31,33,66,67]</sup> The studies did not address functional improvement or long-term effects of BTX-A. Large, well-controlled studies are needed before BTX-A can be considered safe and effective in this condition.

### *Muscle Spasms*

- A spasm is defined as a sudden involuntary contraction of one or more muscles. <sup>[70]</sup>
- Muscle spasms are a potential symptom of spasticity, a condition in which specific muscles are continuously contracted. <sup>[71]</sup> The contraction causes muscles to be stiff or tight and may interfere with movement, speech, and walking.

### *Motor Tics*

- In one small, poor quality trial, BTX-A reduced tic frequency and urge in patients with Tourette Syndrome or Chronic Tic Disorder. <sup>[30]</sup> These reductions were not associated with an overall clinical benefit (measured by the patient's global impression of change).

### *Myofascial Pain*

- BTX-A has not been shown to provide a consistent benefit over placebo in the treatment of myofascial pain. <sup>[59,60,86]</sup>

### *Neurogenic and idiopathic detrusor overactivity/detrusor hyperreflexia*

- Several open-label studies (n=15 to n=200) demonstrated an increase in bladder capacity, a decrease in bladder pressure, and a decrease in incontinence episodes after injection with BTX-A. <sup>[38,39,68]</sup>
- A trial (n=25) comparing BTX-A with intravesical administration of resiniferatoxin in patients who had inadequate response to anticholinergic drugs demonstrated similar results. BTX-A was superior to resiniferatoxin in this study. <sup>[37]</sup>
- A randomized controlled trial in 59 patients demonstrated a statistically significant decrease (approximately 50%) in daily incontinence episodes in patients treated with botulinum toxin type A over the duration of the trial (24 weeks). <sup>[48]</sup>

### *Obesity*

- There is no reliable evidence that BTX-A is useful in reducing body weight in obese patients.
  - \* Two small, poor quality trials failed to show a reduction in body weight after administration of BTX-A. <sup>[53,62]</sup>

- \* A small randomized, double-blind study in 24 morbidly obese patients demonstrated significant difference between BTX-A and saline. However, patients were also maintained on a liquid diet for eight weeks. <sup>[75]</sup>

### *Orthopedic Pain*

- A small, exploratory randomized controlled trial (n=27) reported an improvement in pain scores with BTX-A in patients with plantar fasciitis refractory to other therapies. <sup>[50]</sup> Larger, well-controlled trials are needed to establish safety and effectiveness in this condition and to establish efficacy relative to conventional therapies.
- Several small, poor quality trials evaluated BTX-A in patients with lateral epicondylitis (tennis elbow). <sup>[51,73,86,87]</sup> Consistent benefit has not been demonstrated across trials. Larger, well-controlled trials are needed to establish safety and effectiveness in this condition and to establish efficacy relative to conventional therapies.

### *Pelvic Floor Spasm*

- A randomized controlled trial (n=60) reported a decrease in pelvic floor muscle pressure with BTX-A in women with pelvic floor spasms. There was no significant difference between BTX-A and placebo for reduction in pain scores. <sup>[63]</sup>

### *Piriformis Syndrome*

- Piriformis syndrome is a form of myofascial pain characterized by sciatica and buttock tenderness.
- Few case reports describe the management of piriformis syndrome. <sup>[34]</sup> Physical therapy, steroid injections, surgical dissection or resection of the muscle have been reported to relieve symptoms.
- Well-designed studies using botulinum toxin for this condition have not been conducted. Available evidence consists of small (fewer than 30 patients) open-label, uncontrolled studies. <sup>[2, 78]</sup>

### *Sialorrhea (drooling)*

- There are several small randomized, controlled trials that demonstrate efficacy of BTX-A in patients with sialorrhea secondary to Parkinson's disease. <sup>[40,41,57]</sup>

### *Spasmodic dysphonia*

- A small observational study (n = 43) demonstrated a variable rate of response to BTX-A. [49]
- Patients with more severe symptoms at baseline showed greater improvements after BTX-A treatment. [49]
- Elderly patients had less improvement in symptoms than younger ones. [49]

### Temporomandibular dysfunction (TMJ)

- Several small, uncontrolled (case series) studies have studied BTX-A in the treatment of symptoms (headache, jaw dislocation, etc.) arising from TMJ dysfunction. Larger, well-controlled studies are needed to establish benefit in the treatment of this condition. [88-91]

### *Thoracic outlet syndrome*

- There are no randomized controlled trials evaluating the safety and efficacy of BTX-A in the treatment of thoracic outlet syndrome. Evidence is limited to observational reports and case studies. [79]
- Strengthening exercises, physical therapy and surgery are the standard of care.

### *Tremor*

- BTX-A resulted in significant improvement of postural, but not kinetic hand tremors. [32]
- There is not compelling evidence that BTX-A leads to better functional efficacy for patients. [32]

### *Voice tremor*

- One small, open-label trial in 13 patients suggests efficacy of BTX-A in decreasing the severity voice tremor. [46]
- Well-designed, large-scale studies with repeated injections are necessary to validate potential benefits of BTX-A for treatment of this condition.

## Safety

- Upon review of post-marketing information, the FDA has noted reports of systemic adverse reactions suggestive of botulism following the use of botulinum toxins type A and B. Outcomes include respiratory compromise, hospitalization and death and are most commonly observed in children treated for cerebral palsy-associated limb spasticity.
- The safety, efficacy and dosage of botulinum toxins has not been established for any condition in children less than 12 years of age.

## References

1. J0585 Botulinum Toxin Type A, Medicare Part B Newsletter #178, December 1999, p. 6.
2. Botulinum-A Toxin, BlueCross BlueShield Association Medical Policy #5.01.05, 10/2008.
3. Botox<sup>®</sup> (botulinum toxin type A) Prescribing Information. Allergan, Inc., Irvine, CA. October 2006.
4. Simpson DM. "Clinical trials of botulinum toxin in the treatment of spasticity." *Muscle Nerve Suppl* 1997; 6: S169-75.
5. Bhakta BB, et al. "Impact of botulinum toxin type A on disability and caregiver burden due to arm spasticity after stroke: a randomized double-blind placebo-controlled trial." *J Neurol Neurosurg Psychiatry* 2000; Aug (2):217-21.
6. Lagalla G, et al. "Post-stroke spasticity management with repeated botulinum toxin injections in upper limb." *Am J Phys Med Rehabil* 2000; Jul-Aug; 79:377-84, 391-4.
7. Smith SJ, et al. "A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury." *Clin Rehabil* 2000; Feb 14:5-13.
8. Bianchi L, et al. "Quantitative analysis of the pendulum test: application to multiple sclerosis patients treated with botulinum toxin." *Func Neurol* 1999; Apr-Jun; 14(2): 79-92.
9. Brisinda G, et al. "A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissures." *New Eng J Med* 1999; 341:65-69.
10. Giorgio M, et al. "Botulinum toxin injections in the internal anal fissure for treatment of chronic anal fissure long term results after two different dosage regimens." *Annals of Surgery* 1998; 228:1-10.
11. Treatment of Hyperhidrosis, BlueCross BlueShield Association Policy #8.01.19,2/2008.
12. Schulte-Mattler WJ, et al. "Treatment of tension type headache and botulinum toxin: a pilot study." *Eur J Med Res* 1999; May 26;4:183-6.
13. Davis D, et al. "Significant improvement of stiff-person syndrome after paraspinal injection of botulinum toxin A." *Mov Disord* 1993; July; 8:371-3.

14. The cosmetic use of botulinum toxin, *The Medical Letter*. Vol 41(1057) July 16, 1999;63-4.
15. USP DI<sup>®</sup> and Advice for Patient, Botulinum Toxin Type A, Revised 01/24/2001.
16. Maria G, et al. "A comparison of botulinum toxin and saline for the treatment of chronic anal fissure." *N Eng J Med* 1998;338:217-20.
17. Jost WH. "One hundred cases of anal fissure treated with botulinum toxin." *Dis Colon Rectum* 1997;40:1029-32.
18. Brisinda G, et al. "A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure." *N Engl J Med* 1999;3:341:365-9.
19. Vazzi MF, et al. "Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: A randomized trial." *Gut* 1999;44:231-9.
20. Laskawi R, et al. "Up-to-date report of botulinum A toxin for the treatment in patients with gustatory sweating." *Laryngoscope* 1998;108:381-4.
21. Schnider P, et al. "Double blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms." *Br J Dermatol* 1997;136:548-52.
22. Shelley WB, et al. "Botulinum toxin therapy for palmar hyperhidrosis." *J Am Acad Dermatol* 1998;38:227-9.
23. Naumann M, et al. "Focal hyperhidrosis. Effective treatment with intracutaneous botulinum toxin." *Arch Dermatol* 1998;134:301-4.
24. Levit F. "Treatment of hyperhidrosis by tap water ionophoresis." *Cutis* 1980; 26:192-4.
25. Schachor D, et al. "Endoscopic transthoracic sympathectomy in the treatment of primary hyperhidrosis." *Arch Surg* 1994;129:241-4.
26. 1996 BlueCross BlueShield Association, TEC Assessment; Tab 6.
27. Rollnik JD, et al. "Treatment of tension type headache with botulinum toxin type A: a double-blind placebo controlled study." *Headache* 2000;40:300-5.
28. Brin MF, et al. "Botox for migraine: double-blind, placebo-controlled region-specific evaluation." *Cephalalgia* 2000;20:421-22.
29. Silberstein S, et al. "Botulinum toxin type A as a migraine preventive treatment." *Headache* 2000;40:445-50.
30. Marras C, et al. "Botulinum toxin for simple motor tics. A randomized, double-blind, controlled clinical trial." *Neurology* 2001;56:605-10.
31. Foster L, et al. "Botulinum toxin A and chronic low back pain." *Neurology* 2001;56:1290-3.
32. Brin MF, et al. "A randomized double-masked, controlled trial of botulinum toxin type A in essential hand tremor." *Neurology* 2001;56:1523-8.

33. Foster L, et al. "Botulinum toxin A and chronic low back pain. A randomized, double-blind study." *Neurology* 2001;56:1290-3.
34. Yuen EC, et al. "Entrapment and other focal neuropathies." *Neurol Clin* 1999;617-31.
35. Brashear A, et al. "Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke." *N Engl J Med* 2002;347:395-400.
36. BlueCross BlueShield Association Technology Evaluation Center Bulletin, Volume 19, Number 3, November 11, 2002, pp. 1-5.
37. Giannantoni A, et al. "Intravesical resiniferatoxin versus botulinum-A toxin injections for neurogenic detrusor overactivity: a prospective randomized study." *J Urol* 2004;172:240-3.
38. Riccabona M, et al. "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):845-8.
39. Smith CP, et al. "Botulinum toxin in urology: evaluation using an evidence-based medicine approach." *NCP Urol* 2004;1:31-7.
40. Mancini F, 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;18:685-8.
41. Lipp A, et al. "A randomized trial of botulinum toxin A for treatment of drooling." *Neurology* 2003;61:1279-81.
42. Schulte-Mattler WJ, et al. "Treatment of chronic tension-type headache with botulinum toxin A: a randomized, double-blind, placebo-controlled multicenter study." *Pain* 2004;109:110-4.
43. Ondo WG, et al. "Botulinum toxin A for chronic daily headache: a randomized, placebo-controlled, parallel design study." *Cephalalgia* 2004;24:60-5.
44. Padberg M, et al. "Treatment of chronic tension-type headache with botulinum toxin: a double-blind, placebo-controlled clinical trial." *Cephalalgia* 2004;24:675-80.
45. Unal M, et al. "Effect of botulinum toxin A on nasal symptoms in patients with allergic rhinitis: a double-blind, placebo-controlled clinical trial." *ACTA Otolaryngol* 2003;123:1060-3.
46. Adler C, et al. "Botulinum toxin type A for treating voice tremor." *Arch Neurol* 2004;61:1416-20.
47. Godevenos D, et al. "The treatment of chronic anal fissure with botulinum toxin." *Acta Chir Belg.* 2004;104:577-80.
48. Schurch B, 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.

49. Cannito MP, et al. "Perceptual analyses of spasmodic dysphonia before and after treatment." *Arch Otolaryngol Head Neck Surg.* 2004;130(12):1393-9.
50. Babcock MS, et al. "Treatment of pain attributed to plantar fasciitis with botulinum toxin A: a short-term, randomized, placebo-controlled, double-blind study." *Am J Phys Med Rehabil.* 2005;84(9):649-54.
51. Wong SM, et al. "Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial." *Ann Intern Med.* 2005;143(11):793-7.
52. Lacy BE, et al. "The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus." *Diabetes Care.* 2004;27(10):2341-7.
53. Garcia-Compean D, et al. "Endoscopic injection of botulinum toxin in the gastric antrum for the treatment of obesity. Results of a pilot study." *Gastroenterol Clin Biol.* 2005;29(8-9):789-91.
54. Mathew NT, et al. "Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial." *Headache.* 2005;45(4):293-307.
55. Silberstein SD, 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.
56. Evers 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.
57. Lasgalla G, et al. Botulinum toxin type A for drooling in Parkinson's Disease: a double-blind, randomized placebo-controlled study. *Movement Disorders.* 2006;21(5):704-06.
58. Park DS, et al. Evaluation of short term clinical effects and presumptive mechanism of botulinum toxin type A as a treatment modality of benign prostatic hyperplasia. *Yonsei Med J.* 2006;47(5):706-14.
59. Qerama E, et al. A double-blind, controlled study of botulinum toxin A in chronic myofascial pain. *Neurology.* 2006;67:241-45.
60. Ferrante FM, et al. Evidence against trigger point injection technique for the treatment of cervicothoracic myofascial pain with botulinum toxin type A. *Anesthesiology.* 2005;103:377-83.
61. Cohen JL, et al. Botulinum toxin type A in the treatment of dermatochalasis: an open-label, randomized, dose-comparison study. *Journal of Drugs in Dermatology.* 2006;5:596-606.
62. Gui D, et al. Effect of botulinum toxin antral injection on gastric emptying and weight reduction in obese patients: a pilot study. *Aliment Pharmacol Ther.* 2006;23:675-80.
63. Abbott JA, et al. Botulinum toxin type A for chronic pain and pelvic floor spasm in women. *Obstet Gynecol* 2006;108:915-23.

64. Fruehauf H, et al. Efficacy and safety of botulinum toxin A injection compared with topical nitroglycerin ointment for the treatment of chronic anal fissure: a prospective randomized study. *Am J Gastroenterol* 2006;101:2107-12.
65. Elkind AH, et al. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. *The Journal of Pain*. 2006;7:688-96.
66. Jabbari B, et al. Treatment of refractory, chronic low back pain with botulinum neurotoxin A: an open-label, pilot study. *Pain Medicine*. 2006;7:260-4.
67. Ney JP, et al. Treatment of chronic low back pain with successive injections of botulinum toxin A over 6 months. *Clin J Pain*. 2006;22:363-9.
68. Kajbafzadeh AM, et al. Intravesical injection of botulinum toxin type A: management of neuropathic bladder and bowel dysfunction in children with myelomeningocele. *Urology*. 2006;68:1091-7.
69. American Gastroenterological Association Technical Review on the Management of Hepatitis C. *Gastro* 2006;130:231-64.
70. Stedman's medical dictionary. 27<sup>th</sup> ed. Baltimore: Lippincott Williams & Wilkins;2000. p 1662.
71. National Institute of Neurological Disorders and Stroke [homepage on the internet]. Bethesda, MD. Updated February 14, 2007. Available from: <http://www.ninds.nih.gov/disorders/spasticity/spasticity.htm?css=print>. Accessed: March 5, 2007.
72. Botulinum Toxin Types A and B. Medicare Medical Policy, B2002.20 RI, May 1, 2006.
73. Liu HT et al. Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. *Urology* 2007;70 (3): 463 – 468.
74. Lowe NJ, et al. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. *J Am Acad Dermatol* 2007;56:604-11.
75. Foschi D, et al. Treatment of morbid obesity by intraparietogastric administration of botulinum toxin: a randomized, double-blind, controlled study. *International Journal of Obesity* 2007;31:707-12.
76. Relja M et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A for the prophylaxis of episodic migraine headaches. *Cephalgia* 2007;27:492-503.
77. Aurora SK, et al. Botulinum toxin type A prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. *Headache* 2007;47:486-99.

78. Yoon SJ, et al. Low-dose botulinum toxin type A for the treatment of refractory piriformis syndrome. *Pharmacotherapy* 2007; 27(5):657-65).
79. Jordan SE, et al. Selective botulinum chemodenervation of the scalene muscles for treatment of neurogenic thoracic outlet syndrome. *Ann Vasc Surg.* 2000 Jul;14(4):365-9.
80. Hauser SL, Josephson SA, Harrison TR, Kasper DL, English JD, Braunwald E, Fauci AS, Engstrom JW, Longo DL, editors. *Harrison's Neurology in Clinical Medicine*. 16th ed. New York: McGraw-Hill Professional; 2006.
81. Arts J, Holvoet L, Caenepeel P, Bisschops R, Sifrim D, 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.
82. Friedenberg FK, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. *Am J Gastroenterol.* 2008;103(2):416-23.
83. Silberstein SD, Göbel H, Jensen R, Elkind AH, Degryse 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.
84. Straube A, Empl M, Ceballos-Baumann A, Tölle T, Stefenelli U, et al.; Dysport Tension-Type Headache Study Group. Pericranial injection of botulinum toxin type A (Dysport) for tension-type headache - a multicentre, double-blind, randomized, placebo controlled study. *Eur J Neurol.* 2008;15(3):205-13.
85. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review). *Neurology.* 2008;70:1707-14. Available at [www.neurology.org](http://www.neurology.org).
86. Hayton MJ, Santini AJ, Hughes PJ, Frostick SP, Trail IA, 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.
87. Keizer SB, Rutten HP, Pilot P, Morré HH, v Os JJ, et al. Botulinum toxin injection versus surgical treatment for tennis elbow: a randomized pilot study. *Clin Orthop Relat Res.* 2002;(401):125-31.
88. Karacalar A, Yilmaz N, Bilgici A, Baş B, Akan H. Botulinum toxin for the treatment of temporomandibular joint disk disfigurement: clinical experience. *J Craniofac Surg.* 2005 May;16(3):476-81.
89. Ziegler CM, Haag C, Mühling J. Treatment of recurrent temporomandibular joint dislocation with intramuscular botulinum toxin injection. *Clin Oral Investig.* 2003;7(1):52-5.
90. 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.

91. 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.
92. Brashear A, Truong B, Charles D, et al. A randomized, double-blind, placebo-controlled study of intramuscular BOTOX® for the treatment of cervical dystonia [abstract]. *Mov Disord* 1998;13:276.

Cross References	
1.	Botulinum Toxin, Blue Cross BlueShield Association Medical Policy, 5.01.05. Review Date: 10/2008.
2.	Treatment of Hyperhidrosis, BlueCross BlueShield Association Medical Policy 8.01.19. Review Date: 2/2008.
3.	Surgical Treatments for Hyperhydrosis, Regence Medical Policy; Med 165.
4.	Myobloc <sup>®</sup> , botulinum toxin type B dru045
5.	Cosmetic and Reconstructive Surgery, Surgery Section; Medical Policy No. 12.

Codes	Number	Description
HCPCS	J0585	Botulinum toxin, type A, per unit