



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject OnabotulinumtoxinA
(Botox® A)**

Effective Date..... 8/15/2009
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Coverage Policy Number 5018

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Hyperlink to Related Coverage Policies

[Botulinum Toxin Type B \(Myobloc®\)](#)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

Coverage Policy

CIGNA covers onabotulinumtoxinA (Botox® A) as medically necessary for ANY of the following indications:

- **dystonias, spasticities, and neuro-ophthalmological conditions, including:**
 - **cervical dystonia**, including spasmodic torticollis, causing persistent pain or interfering with the ability to perform age-related activities of daily living
 - **focal dystonias**
 - treatment of blepharospasm
 - focal hand dystonia (e.g. writer's cramp) causing persistent pain or interfering with the ability to perform age-related activities of daily living
 - adductor spasmodic dysphonia/laryngeal dystonia
 - jaw-closing oromandibular dystonia causing **ANY** of the following:
 - persistent pain
 - interference with nutritional intake (e.g. masticatory dysfunction that results in weight loss or malnutrition)

- significant speech impairment/interference with the ability to communicate effectively
 - Meige's syndrome/cranial dystonia (i.e. blepharospasm with jaw-closing oromandibular cervical dystonia) when jaw-closing oromandibular dystonia is causing any one of the following
 - persistent pain
 - interference with nutritional intake (e.g. masticatory dysfunction that results in weight loss or malnutrition)
 - significant speech impairment/interference with the ability to communicate effectively
- **spastic conditions**
 - cerebral palsy (including spastic equinus foot deformities)
 - cerebrovascular accident
 - localized adductor muscle spasticity in multiple sclerosis
 - spinal cord injury
 - traumatic brain injury
 - hereditary spastic paraplegia
- **hemifacial spasms/seventh cranial nerve palsy/gaze palsies** causing persistent pain or vision impairment
- **strabismus disorders in adults, in situations when:**
 - (a) **ONE** of the following is present:
 - horizontal strabismus up to 50 prism diopters
 - vertical strabismus
 - persistent sixth nerve palsy of one month or longer duration
 - AND**
 - (b) **ONE** the following is present:
 - diplopia
 - impaired depth perception
 - impaired peripheral vision
 - impaired ability to maintain fusion
- **strabismus disorders in children** to achieve normal binocular motor alignment
- **gastrointestinal conditions, including:**
 - **primary esophageal achalasia in individuals who have ANY of the following:**
 - concomitant illness and/or who are at high risk for complications such as esophageal reflux or perforation
 - have not responded to prior myotomy or dilation
 - have a history of perforation caused by previous pneumatic dilatation
 - have an epiphrenic diverticulum
 - **chronic anal fissure** in individuals who have failed conventional non-surgical treatment (e.g. nitrate preparations, sitz baths, stool softeners, bulk agents, diet modifications)
- **hyperhidrosis** when **EITHER** of the following indications are met:
 - primary axillary hyperhidrosis that is inadequately managed with a prescription topical agent
 - palmar hyperhidrosis **OR** gustatory sweating (Frey's syndrome, diabetic gustatory sweating) when the condition is refractory to conventional medical treatment including an attempt at both topical and pharmacotherapy (unless clinically contraindicated) **AND** when **ONE** of the following criteria is met:

- the condition is significantly interfering with the individual's ability to perform age-appropriate activities of daily living.
- the condition is causing persistent or chronic cutaneous conditions such as skin maceration, dermatitis, fungal infections and secondary microbial conditions.
- **disabling essential tremor including head, neck, hand, and voice tremor**
- **excessive glandular secretion refractory to pharmacotherapy (including anticholinergics) including EITHER of the following:**
 - cholinergic-mediated secretions associated with various types of fistulas (e.g. parotid gland, pharyngocutaneous)
 - ptyalism/sialorrhea (excessive salivation) associated with parkinsonism and cerebral palsy
- **voiding dysfunction associated with EITHER of the following:**
 - intracranial lesions or cerebrovascular accident-induced voiding difficulty
 - detrusor sphincter dyssynergia due to spinal cord injury
- **prophylaxis of migraine AND failure, contraindication, or intolerance to two migraine prophylaxis medications (e.g. beta-blockers, calcium channel blockers, tricyclic antidepressants or anticonvulsant medications)**

When criteria are met for coverage, approval consists of a quantity of four (4) treatments in a 12 month period (one (1) treatment every 90 days)

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

CIGNA does not cover onabotulinumtoxinA (Botox[®] A) because it is considered experimental, investigational, or unproven (this list may not be all-inclusive).

- anismus
- chronic constipation
- chronic pain including **ANY** of the following
 - low back pain
 - mastectomy reconstruction pain
 - hemorrhoid pain
 - myofascial pain
 - chronic prostate pain
 - tennis elbow
 - chronic neck pain
- temporomandibular dysfunction or chronic orofacial pain
- headache (tension-type headache, chronic daily headache)
- rhinitis
- tics
- paralytic scoliosis
- diabetic gastroparesis
- sphincter of Oddi dysfunction
- vaginismus
- voiding dysfunction associated with **ANY** of the following:
 - benign prostatic hyperplasia
 - detrusor hyperreflexia due to myelomeningocele
 - urge incontinence refractory to anticholinergic therapy

General Background

FDA Approved Indications

Botox is indicated for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia. Botox is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents. Botox is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above. The efficacy of Botox treatment in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been established. Botox is ineffective in chronic paralytic strabismus except when used in conjunction with surgical repair to reduce antagonist contracture.

FDA Recommended Dosing

Cervical Dystonia

The mean Botox dose administered to patients in the phase 3 study was 236 Units. The Botox dose was divided among the affected muscles. Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response and adverse event history. The initial dose for a patient without prior use of Botox should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscles to 100 Units or less may decrease the occurrence of dysphagia. Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection.

Primary Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Blepharospasm

The initial recommended dose of Botox is 1.25 - 2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient. The cumulative dose of Botox treatment in a 30-day period should not exceed 200 Units.

Strabismus

Botox is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. The volume of Botox injected for treatment of strabismus should be between 0.05 - 0.15 mL per muscle. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 - 2.5 Units in any one muscle. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 - 5.0 Units in any one muscle. For persistent VI nerve palsy of one month or longer duration: 1.25 - 2.5 Units in the medial rectus muscle. Subsequent doses for residual or recurrent strabismus - it is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose. The maximum recommended dose as a single injection for any one muscle is 25 Units.

Pharmacology

OnabotulinumtoxinA (Botox A) is available as Botox and Botox Cosmetic. Botulinum toxins work in the peripheral and autonomic nervous systems by preventing the release of acetylcholine. This results in disrupted neurotransmission and muscle paralysis. Botulinum toxin doses are expressed in units of biologic activity, with one unit corresponding to the lethal dose for female Swiss-Webster mice.

OnabotulinumtoxinA is not expected to be present in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, sub-clinical systemic effects have been shown by single fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.

The different botulinum formulations are not interchangeable, as assays measuring the lethal dose differ. Pharmacokinetic data such as absorption, distribution, metabolism, and elimination are not available for Botox A. The recommended dosage and frequency of administration for Botox should not be exceeded. Risks resulting from administration at higher dosages are not known.

Clinical Efficacy Cervical Dystonia

A phase 3 randomized, multi-center, double blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received Botox in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of Botox. There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the Botox group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65.

Primary Axillary Hyperhidrosis

The efficacy and safety of Botox for the treatment of primary axillary hyperhidrosis were evaluated in a randomized, multi-center, double-blind, placebo-controlled study. 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of Botox (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% in the Botox group and 36% in the placebo group, $p < 0.001$.

Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label uncontrolled study, 27 patients with essential blepharospasm were injected with 2.0 Units of Botox at each of six sites on each side. One patient had not received any prior treatment. Twenty-six of the patients had not responded to therapy with benzotropine mesylate, clonazepam and/or baclofen. Three of the 26 patients continued to experience spasms following muscle stripping surgery. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The mean dystonia score improved by 72%, the self-assessment score rating improved by 61%, and a videotape evaluation rating improved by 39%. The effects of the treatment lasted a mean of 12.5 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12.5 weeks prior to the need for re-treatment.

Strabismus

It is postulated that when used for the treatment of strabismus, the administration of Botox affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the muscle's antagonist; it was on the basis of this hypothesis that clinical studies were conducted. Six hundred seventy-seven patients with strabismus treated with one or more injections of Botox were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection. These results are consistent with results from additional open label trials which were conducted for this indication.

Clinical Efficacy of Off-Label Indications

Based on peer-reviewed literature and the American Hospital Formulary Service Drug Information (AHFS DI), there is sufficient evidence to support the use of onabotulinumtoxinA for all of the indications included in the criteria for the coverage policy. Most supporting data for off-label uses are from one or two trials. Few trials had active comparators and most are placebo-controlled or case series data.

Voiding Dysfunction

Available data demonstrate positive results for Botox A treatment for treatment of voiding dysfunction caused by the following conditions:

- **Intracranial Lesions or Cerebrovascular Accident-Induced Voiding Difficulty:** Chen and Kuo (2004) also showed positive results with Botox A when comparing Botox A and no treatment in patients with urinary problems due to intracranial lesions or cerebrovascular accidents. Patients who received a urethral injection of Botox A showed improved voiding pressure and increased maximum urine flow rates (+3.1 mL/sec) compared to baseline (p<0.05). No adverse effects or withdrawals were reported.
- **Detrusor Sphincter Dyssynergia Due to Spinal Cord Injury:** de Seze et al. (2002) compared injections of lidocaine 0.5% and Botox A in patients with detrusor sphincter dyssynergia. After 30 days, patients treated with Botox A decreased their post-void residual by 159 mL compared to an increase of 50 mL in patients treated with lidocaine (p<0.01). More patients receiving Botox A improved on Blaivas' classification of detrusor sphincter dyssynergia compared to patients treated with lidocaine (p<0.04). Patients experienced an equal amount of incontinence between groups and no patients withdrew from the study.

Headache/Migraine

Table 1 provides the summary of most current published clinical trials evaluating the safety and efficacy of botulinum toxin A for the prophylactic treatment of various types of headache.

Table 1

Source and Objective	Method / Study Design	Outcome	Grade*
<p>Source: Cady et al. Headache. 48(6):900-913, June 2008.</p> <p>Objective: To examine the efficacy and safety of and satisfaction with onabotulinumtoxinA for prophylactic treatment of headache in patients previously failing</p>	<p>- randomized, double-blind, single-center, placebo-controlled study (months 1 to 3) of BoNTA with a cross-over to open-label BoNTA treatment (months 4 to 6). [N=73 subjects screened, 61 (40 BoNTA; 21 placebo)</p> <p>- Pt population: with disabling headache (International Headache Society, International Classification of Headache Disorders [ICHD-I] diagnosis 1.1,</p>	<p>-No statistical significance at months 1 to 3 for the number of headache episodes or days.</p> <p>- During the open-label study, BoNTA-treated subjects had a decrease in the number of headache episodes at months 5 and 6 (P < .05) vs baseline for both) and headache days at months 5 and 6 (P < .05 vs baseline).</p> <p>- A decrease in Headache Impact Test (HIT-6) scores was significantly greater for BoNTA-treated subjects than for placebo-treated subjects at month 3 (P = .0466).</p> <p>- Within-group decreases in HIT-6 scores were significant in BoNTA-treated subjects during each month of the blinded trial (for months 1 to 3, respectively; P < .0001 for all vs baseline) and throughout the open-label portion of the study</p>	1

prophylaxis because of issues pertaining to compliance.	1.2, 1.7, or 2.2, and Headache Impact Test [HIT]-6 scores ≥ 56) previously failing prophylaxis because of compliance, tolerability, or adherence issues -Primary endpoint: reduction of the number of headache episodes or days -Secondary endpoint: headache severity	(months 4 to 6, respectively; $P < .01$ for all vs baseline). - At 3 months, BoNTA was significantly better than placebo ($P = .001$) in the reduction of Migraine Disability Assessment (MIDAS) total score. The change from baseline in the MIDAS total scores was significant in BoNTA-treated subjects ($P < .0001$) but not in placebo recipients. - BoNTA-treated subjects showed improvement in 11 of 13 and 7 of 13 assessments of treatment satisfaction in Migraine Impact Questionnaire (MIQ) at months 3 and 6, respectively, while the placebo group showed no improvement at any measured time interval in the study. - At month 3 (blinded period), there were no treatment-related AEs reported in both groups.	
Source: Blumenfeld, et al. Headache. 48(2):210-220, February 2008. Objective: To compare the efficacy and safety of onabotulinumtoxinA and divalproex sodium as prophylaxis in reducing disability and impact associated with migraine	- randomized, double-blind, single-center prospective study. -59 patients received either BoNTA 100 U/placebo-DVPX bid or placebo-BoNTA/DVPX 250 mg bid. BoNTA/placebo injections were given at Day 0 and at Month 3. Patients were evaluated at Months 1, 3, 6, and 9.	- Both treatments showed significant improvements in disability scores and reductions in headache days and headache index. - A trend to decreased headache severity was observed with BoNTA. - A greater percentage of DVPX patients reported adverse events possibly related to treatment (DVPX 75.8% vs BoNTA 50%, $P = .04$) and discontinued because of adverse events (DVPX 27.6% vs BoNTA 3.3%, $P = .012$).	1
Source: Freitag, et al Headache. 48(2):201-209, February 2008. Objective: To examine the effects of onabotulinumtoxinA in the Treatment of Chronic Migraine Without Medication Overuse.	- Double-blind placebo-controlled randomized trial of onabotulinumtoxinA 100 units administered in a fixed dose - Patients: A total of 60 patients were randomized and 41 patients were treated with the study medication or placebo. Five patients failed to complete the study, which lasted 4 months after the study medication was injected.	- OnabotulinumtoxinA was statistically superior to placebo for the primary endpoint of reduction in headache episodes and the secondary endpoints including total headache days, headache index, and quality of life measures - 6 patients on onabotulinumtoxinA compared with 3 patients on Placebo had at least a 50% reduction in their episodes. - It showed numerical superiority to placebo for acute medication use and Disability Assessment Scores. - similar adverse events were report for both treatment groups.	1

*Grade 1 Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals

The results from randomized, double-blind, and placebo-controlled published studies show the efficacy of BoNT-A injection for the prophylactic treatment of migraine headache. Future clinical trials appear warranted to evaluate the use of BoNT-A injection for treatment of migraine, chronic tension-type headache, and chronic daily headache.

Sialorrhea

Two trials are available evaluating Dysport® (abobotulinumtoxinA) for the treatment of sialorrhea in patients with Parkinson's disease. Observational data are available comparing Botox A and scopolamine for the treatment of sialorrhea in patients with cerebral palsy.

- **Parkinson's Disease Sialorrhea:** Clinical trial data show that injections of the parotid glands with a onabotulinumtoxinA decrease sialorrhea by 20–50%. Adverse effects include dry mouth, worsened gait, diarrhea, and neck pain. No patients withdrew from these studies due to adverse effects.
- **Cerebral Palsy Sialorrhea:** Jongerius et al. (2004) compared transdermal scopolamine and Botox A in children with cerebral palsy and severe sialorrhea. Both scopolamine and Botox A therapy reduced the drooling quotient by 15–20 points ($p=0.0001$). More patients receiving

scopolamine (82%) had anticholinergic adverse effects compared to patients receiving Botox A (5%). Four patients withdrew due to side effects from scopolamine; no patients withdrew due to adverse effects from Botox A.

Ongoing Studies for Investigational Uses

Chronic Pain

Nine trials are available evaluating the effectiveness of Botox A for the treatment of patients with different types of chronic pain. These data show positive results for Botox A in patients with low back pain, mastectomy reconstruction pain, hemorrhoid pain, chronic prostate pain, and myofascial pain syndrome. Botox A therapy is not effective at relieving neck pain and is equivalent to surgery in patients with tennis elbow. All trials reported few or no adverse effects, and no patients withdrew due to side effects.

- **Low Back Pain:** Foster et al. (2001) showed that after three and eight weeks after Botox A injections into the sacral region, low back pain decreases by 50% as measured via visual analog scale (VAS). Patients also showed improvements on the Oswestry Low Back Pain Questionnaire at eight weeks, with 66.7% of patients treated with Botox A showing some improvement from baseline compared to 18.8% of patients treated with placebo ($p=0.011$).
- **Mastectomy Reconstruction Pain:** Layeeque et al. (2004) showed a significant decrease in immediate postoperative pain (mean VAS score 3) in patients who received a Botox A infiltration compared to patients who received standard therapy (mean VAS score 6.8) ($p<0.001$). Patients in the Botox A group also had decreased pain during tissue expansion ($p\leq 0.009$).
- **Hemorrhoid Pain:** Davies et al. (2003) showed that Botox A injections into the internal anal sphincter in patients undergoing Milligan-Morgan hemorrhoidectomy had lower pain scores compared to patients receiving placebo, $p < 0.02$. No differences were noted in the amount of postoperative analgesic required.
- **Myofascial Pain:** Porta (2000) compared trigger point injections of bupivacaine and either Botox A or methylprednisolone in patients with chronic myofascial pain. At baseline, patients in the Botox A group had higher pain scores than the methylprednisolone group, $p = 0.006$. At day 60, there were significant differences in pain scores (Botox A -5.5, methylprednisolone -2.5, $p<0.0001$), but not at day 30.
- **Chronic Prostate Pain:** Zermann et al. (2000) reported case series data that Botox A perisphincteric injection in patients with chronic prostate pain can reduce pain (VAS, 10 cm) by -5.6 compared to baseline (p =not reported). These authors also noted positive improvements compared to baseline in post-void residuals, average urine flow, peak urine flow, urethral sphincter closing pressure, and functional urethral length ($p<0.001$).
- **Tennis Elbow:** Keizer et al. (2002) found no differences in pain, range of motion, or patient satisfaction between patients who received one or two injections of Botox A compared to patients who had surgery (Hohmann modified release). Patients who underwent surgery used less sick leave at three months than patients receiving Botox A injections ($p<0.01$), but there were no differences at six, 12, and 24 months. These authors did not perform a power calculation to determine if their sample size was sufficient to detect a difference.
- **Chronic Neck Pain:** Three trials are available comparing Botox A injections to placebo in patients with chronic neck pain. No trial showed a difference between groups for reduction in neck pain. These trials may have had insufficient sample size to detect a difference. No differences were found between groups using the Vernon-Mior Score, Neck Pain and Disability Scale, Global Assessment Scale, and the SF-36 health survey.

Temporomandibular Dysfunction or Chronic Orofacial Pain

Two trials are available evaluating Botox A in patients with chronic orofacial pain. Nixdorf et al. found no differences between Botox A and placebo for relief of pain. von Lindern et al. (2003) showed a decrease

in pain scores of 3.2 on a 10 cm visual analog scale for patients treated with Botox A and a decrease of 0.4 for patients treated with placebo ($p < 0.01$). Three case series reports are available evaluating Botox A in patients with temporal mandibular dysfunction. These data show that Botox A treatment can reduce pain scores (VAS, 10 cm) by at least three points compared to baseline ($p < 0.05$).

Rhinitis

Two trials are available comparing Botox A and placebo injections for patients with intrinsic rhinitis and allergic rhinitis. Patients with intrinsic rhinitis treated with Botox A had decreased rhinorrhea during the first four weeks of follow-up compared to patients treated with placebo ($p < 0.05$). No differences were noted between groups during the remaining 20 weeks of follow-up. No differences were noted between groups for sneezing and nasal stuffiness symptoms. Patients with allergic rhinitis treated with Botox A had decreased rhinorrhea, nasal obstruction, and sneezing compared to patients treated with placebo. Itching scores did not differ favoring Botox A treatment after two weeks of treatment. No adverse effects or withdrawals were reported in either trial.

Treatment of Tics

One trial is available comparing Botox A and placebo in patients with one or more motor tics due to Tourette syndrome or idiopathic tic disorder. Botox A treatment decreased the number of tics performed per minute by 39%, while patients treated with placebo experienced an increase in tic performance of 5.8% ($p < 0.05$). No differences between groups were noted in the Tourette Syndrome Global Score, Yale Global Tic Severity Scale, or Unified Tic Rating Scale. Approximately 50% of patients experienced muscle weakness, and 10% experienced motor restlessness and the emergence of new tics. One patient withdrew from each group for unspecified reasons.

Paralytic Scoliosis

Nuzzo et al. (1997) administered Botox A to 12 children with paralytic scoliosis requiring surgical intervention. Botox A therapy improved spine curvature from 9–51 degrees and no child worsened.

Diabetic Gastroparesis

Two case series showed positive results with Botox A therapy improving gastric emptying by 112 minutes and subjective symptom scores from baseline ($p < 0.05$).

Sphincter of Oddi Dysfunction

Two case series with Dysport showed some improvement with Botox A therapy decreasing the return of biliary colic or acute pancreatitis.

Vaginismus

In a controlled study from Egypt, 8 women were injected with Botox (50 IU) for vaginismus into the bulbospongiosus muscles, and 5 matched women injected with saline. All women given Botox were able to have intercourse, whereas the controls did not improve during a follow up period of 10.2 +/- 3.3 months. Of the patients given Botox none required re-injection and there was no recurrence or complication during the follow up period. The authors conclude that the technique is simple, easy, cost-effective, not time-consuming and can be achieved on an outpatient basis.

Voiding Dysfunction

Available data demonstrate positive results for Botox A treatment for treatment of voiding dysfunction caused by the following conditions:

- **Benign Prostatic Hyperplasia:** Maria et al. (2003) compared Botox A and placebo in patients with symptomatic benign prostatic hyperplasia. Patients treated with Botox A had decreased American Urological Index scores (65% to 54%) compared to patients treated with placebo who had no changes ($p < 0.05$). Patients treated with Botox A also had decreased post-void residual volumes (83% to 60%) compared to patients treated with placebo who had no changes ($p < 0.05$). No adverse effects or withdrawals were reported.

- **Detrusor Hyperreflexia Due to Myelomeningocele:** Schulte-Baukloh et al. (2002) administered bladder injections of Botox A to 17 children with detrusor hyperreflexia. These results showed that maximum bladder capacity increased by 56%, maximum detrusor pressure decreased by 32.6%, and detrusor compliance increased by 121% compared to baseline values ($p < 0.05$). No adverse effects or withdrawals were reported.
- **Urge Incontinence Refractory to Anticholinergic Therapy:** Rapp et al. (2000) administered bladder injections of Botox A to a series of patients with urge incontinence and showed that 34% of patients achieved a complete response, 26% had slight improvement, and 40% had no improvement compared to baseline values ($p = \text{not reported}$). Patients showed improvements on the Incontinence Impact Questionnaire and Urogenital Distress Inventory scales compared to baseline ($p < 0.003$). Approximately 20% of patients experienced mild hematuria, pelvic pain, and dysuria; however, no patients withdrew due to these adverse effects.

Adverse Reactions

In April 2009 the FDA announced that safety label changes including a boxed warning and a Risk Evaluation and Mitigation Strategy (REMS) will now be required for all botulinum toxin products. The agency took the action because of two main reasons. The first one is the potential for serious risks that may occur from the spread of the botulinum toxin beyond the injection site. The second reason is associated with the lack of interchangeability among the three licensed botulinum toxin products. When the botulinum toxin spreads beyond the area of injection, symptoms similar to botulism may occur. These symptoms include unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids. This “spreading effect” has been reported in both children and adults. It has been reported most often in children with cerebral palsy being treated with the products for muscle spasticity. Treatment of muscle spasticity is an off-label use of the drug. The “spreading effect” has been reported in patients being treated for both approved and unapproved uses.

Therapy with Botox A is generally well-tolerated. The most common side effects of Botox A therapy are muscle weakness and injection site pain. Theoretical drug interactions may occur with concomitant use of neuromuscular blockers, but the clinical significance of this interaction is unknown. Serious and/or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent and consequently the causal agent cannot be reliably determined. If such a reaction occurs, further injection of Botox should be discontinued and appropriate medical therapy immediately instituted.

Contraindications

Botox is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
64612	Chemodenervation of muscle(s); muscle(s) innervated by facial nerve (eg, for blepharospasm, hemifacial spasm)
64613	Chemodenervation of muscle(s); neck muscle(s) (eg, for spasmodic torticollis, spasmodic dysphonia)

64614	Chemodenervation of muscle(s); extremity(s) and/or trunk muscle(s) (eg, for dystonia, cerebral palsy, multiple sclerosis)
64650	Chemodenervation of eccrine glands; both axillae
64614	Chemodenervation of eccrine glands; other area(s)(e.g.: scalp, face, neck), per day
67345	Chemodenervation of extraocular muscle

HCPCS Codes	Description
J0585	OnabotulinumtoxinA , per unit

ICD-9-CM Diagnosis Codes	Description
333.1	Essential and other specified forms of tremor
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
334.1	Hereditary spastic paraplegia
340	Multiple sclerosis
341.0-341.9	Other demyelinating diseases of central nervous system
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
343.8	Other specified infantile cerebral palsy
343.9	Unspecified infantile cerebral palsy
346.00-346.93	Migraine
350.8	Other specified trigeminal nerve disorders
351.8	Other facial nerve disorders
368.33	Fusion with defective stereopsis
378.00-378.73	Strabismus and other disorders of binocular eye movements
478.75	Laryngeal spasm
530.0	Achalasia and cardiospasm
565.0	Anal fissure
596.55	Detrusor sphincter dyssynergia
705.21	Primary focal hyperhidrosis
705.22	Secondary focal hyperhidrosis
723.5	Torticollis, unspecified
736.72	Equinus deformity of foot, acquired

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
307.20	Tic disorder, unspecified
307.21	Transient tic disorder
307.22	Chronic motor or vocal tic disorder
307.23	Tourette's disorder
307.81	Tension headache
333.3	Tics of organic origin
339.10- 339.12	Tension type headache
346.00	Classical migraine without mention of intractable migraine
346.01	Classical migraine with intractable migraine, so stated
346.10	Common migraine without mention of intractable migraine
346.11	Common migraine with intractable migraine, so stated
346.90	Unspecified migraine without mention of intractable migraine
346.91	Unspecified migraine with intractable migraine, so stated
350.1	Trigeminal neuralgia
455.1	Internal thrombosed hemorrhoids
455.2	Internal hemorrhoids with other complication
455.4	External thrombosed hemorrhoids
455.5	External hemorrhoids with other complication
455.7	Unspecified thrombosed hemorrhoids
455.8	Unspecified hemorrhoids with other complication
472.0	Chronic rhinitis
477.0	Allergic rhinitis due to pollen
477.1	Allergic rhinitis, due to food
477.2	Allergic rhinitis due to animal (cat) (dog) hair and dander
477.8	Allergic rhinitis due to other allergen
477.9	Allergic rhinitis, cause unspecified
524.60	Unspecified temporomandibular joint disorders
524.62	Arthralgia of temporomandibular joint
536.3	Gastroparesis
576.5	Spasm of sphincter of Oddi
600.01	Hypertrophy (benign) of prostate with urinary obstruction and other lower urinary tract symptoms [LUTS]
723.1	Cervicalgia
724.2	Lumbago
726.32	Lateral epicondylitis of elbow
784.0	Headache
788.20	Unspecified retention of urine
788.21	Incomplete bladder emptying
788.29	Other specified retention of urine

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	8/15/2008	5018	OnabotulinumtoxinA (Botox [®] A)
Great-West Healthcare	12/2006	P04.104.2	Botox, Myobloc

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