



BlueCross BlueShield
of Alabama

Name of Policy:

Treatment of Hyperhidrosis

Policy #: 086
Category: Therapy

Latest Review Date: November 2009
Policy Grade: B

Background:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts to have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

- 1. The technology must have final approval from the appropriate government regulatory bodies;*
- 2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
- 3. The technology must improve the net health outcome;*
- 4. The technology must be as beneficial as any established alternatives;*
- 5. The improvement must be attainable outside the investigational setting.*

Description of Procedure or Service:

Hyperhidrosis may be defined as excessive sweating, beyond a level required to maintain normal body temperature in response to heat exposure or exercise. Hyperhidrosis can be classified as either primary or secondary. Primary hyperhidrosis is idiopathic in nature, typically involving the hands (palmar), feet (plantar), or axillae. Secondary hyperhidrosis can result from a variety of drugs, such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), or underlying diseases/conditions, such as febrile diseases, diabetes mellitus, or menopause. Gustatory hyperhidrosis is an unusual iatrogenic cause of facial hyperhidrosis in response to hot or spicy foods, resulting from surgery to the parotid gland and subsequent aberrant regenerating parasympathetic fibers.

The consequences of hyperhidrosis are primarily psychosocial in nature. Excessive sweating may be socially embarrassing (i.e., limiting the ability to shake hands) or interfere with certain professions. For example, palmar hyperhidrosis may preclude artwork, working with electrical components, or playing certain musical instruments. In addition, hyperhidrosis may require

several changes of clothing a day; excessive sweating may also result in staining of clothing or shoes.

Treatment of secondary hyperhidrosis naturally focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment of menopausal symptoms. A variety of therapies have been investigated for primary hyperhidrosis, including topical therapy with aluminum chloride or tanning agents, iontophoresis, botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands. Botulinum toxin has also been investigated as a treatment of secondary gustatory hyperhidrosis. In terms of botulinum toxin, this policy only discusses its use as a treatment of hyperhidrosis.

On February 8, 2008, the FDA issued an Early Communication about the Ongoing Safety Review; Botox and Botox Cosmetic FDA (botulinum toxin type A) and Myobloc (botulinum type B). The FDA has received reports of systemic adverse reactions including respiratory compromise and death following the use of botulinum toxins types A and B for both FDA-approved and unapproved uses. The reactions reported are suggestive of botulism, which occurs when botulinum toxin spreads in the body beyond the site where it was injected. The most serious cases had outcomes that included hospitalization and death, and occurred mostly in children treated for cerebral palsy-associated limb spasticity. Use of botulinum toxins for treatment of limb spasticity (severe arm and leg muscle spasms) in children or adults is not an approved use in the United States. The communication stated; “The safety, efficacy and dosage of botulinum toxins have not been established for the treatment of limb spasticity of cerebral palsy or for use in any condition in children less than 12 years of age”. The FDA will update this document when additional information or analyses become available.

Policy:

Effective for dates of service on or after January 20, 2010:

Primary Focal Hyperhidrosis

Primary focal hyperhidrosis is defined as excessive sweating induced by sympathetic hyperactivity in selected areas that is not associated with an underlying disease process. The most common locations are underarms (axillary hyperhidrosis), palms (palmar hyperhidrosis), soles (plantar hyperhidrosis) or face (craniofacial hyperhidrosis).

The following **treatments for hyperhidrosis meet Blue Cross and Blue Shield of Alabama coverage when there is documentation of functional impairment or medical complications related to the hyperhidrosis. The specific treatments and additional criteria for coverage is listed below by body area.**

Focal Regions

Axillary

The following treatments for the **axillary meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:**

- Aluminum chloride 20% solution;

- Botulinum (intra-dermal injection) for severe primary axillary hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older;
- Endoscopic transthoracic sympathectomy (ETS) and surgical excision of axillary sweat glands, if conservative treatment (i.e., aluminum chloride or botulinum type A, individually and in combination) has failed

The following treatments for the **axillary do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered **investigational**:

- Axillary liposuction
- Iontophoresis

Palmar

The following treatments for the **palmar meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

- Aluminum chloride 20% solution;
- Botulinum (intra-dermal injection) for severe primary palmar hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older;
- Endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride or botulinum type A, individually and in combination) has failed

Treatment of hyperhidrosis of the **palmar focal region does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** for the treatment of **iontophoresis**.

Plantar

Treatment of hyperhidrosis of the **plantar focal region meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of **aluminum chloride 20% solution**.

The following treatments for the **plantar focal region do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational**:

- Botulinum
- Iontophoresis
- Lumbar sympathectomy

Craniofacial

The following treatments for the **craniofacial focal region meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

- Aluminum chloride 20% solution;

- Endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride) has failed

The following treatments for the **craniofacial** focal region **do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational**:

- Botulinum
- Iontophoresis

Secondary Hyperhidrosis

Secondary hyperhidrosis is excessive sweating that can be generalized or craniofacial sweating and may occur as a result of olfactory or gustatory stimuli, neurologic lesions, intrathoracic neoplasms, Raynaud’s disease and Frey’s syndrome.

Secondary Gustatory Hyperhidrosis

The following treatments **meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage **for the treatment of severe gustatory hyperhidrosis**:

- Aluminum chloride 20% solution
- Surgical options (i.e., tympanic neurectomy), if conservative treatment has failed.

The following treatments **do not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered **investigational** as a **treatment for severe gustatory hyperhidrosis** including, but not limited to:

- Botulinum toxins are considered **investigational** for treatment of gustatory hyperhidrosis.
- Iontophoresis

Effective for dates of service on or after December 16, 2005 through January 19, 2010:

Treatment of primary hyperhidrosis and gustatory hyperhidrosis that has failed conservative therapy such as prescription strength aluminum chloride, **meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage of botulinum toxin or surgical therapy.

Axillary liposuction does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage based on an evidence-based approach and are considered **investigational** as a treatment for primary hyperhidrosis. The surgical procedure should be a last effort after all other methods have failed to relieve the complication or functional impairment.

Iontophoresis meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage of the treatment of palmar, plantar, and axillary hyperhidrosis.

For dates of service prior to December 16, 2005:

Primary Hyperhidrosis

Treatment of primary hyperhidrosis, including aluminum chloride, botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands **meets** Blue Cross and Blue Shield of Alabama's medical criteria for coverage only in the small subset of patients with medical complications, such as skin maceration with secondary infections or significant functional impairments.

Secondary Gustatory Hyperhidrosis

Botulinum toxin is considered an effective treatment of gustatory hyperhidrosis. (Please refer to the Botox policy for additional information).

Iontophoresis and axillary liposuction do not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage based on an evidence-based approach and are considered **investigational** as a treatment for primary hyperhidrosis. The surgical procedure should be a last effort after all other methods have failed to relieve the complication or functional impairment

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

Key Points:

Aluminum chloride

Aluminum chloride is a common component of over-the-counter antiperspirants, although a prescription product is available (Drysol). Although the mechanism is unclear, aluminum chloride is associated with atrophy of the secretory cells seen in eccrine sweat glands. Aluminum chloride is predominantly used to treat axillary hyperhidrosis and not palmar or volar hyperhidrosis.

Iontophoresis

Iontophoresis is a technique that involves the use of an electric current to introduce various ions through the skin.

The mechanism of action is not precisely known, but is thought to be related to plugging of the sweat gland pores. The typical device consists of trays containing electrodes. Prior to using, the trays are filled with tap water, the patient inserts the hands or feet or positions the device in the axilla, and the current is turned on. Patients are treated for approximately 20 minutes, with treatments every 2 to 3 days for 5 to 10 sessions before an effect is observed. Maintenance therapy may be applied every 2 weeks after initial therapy.

Iontophoresis in conjunction with tap water or anticholinergic agents is a long-standing treatment of palmar or plantar and more recently axillary idiopathic hyperhidrosis, with a reported success

rate of up to 85%. (1). However, the published literature regarding iontophoresis as a treatment of hyperhidrosis is sparse. A 2003 TEC Assessment on iontophoresis concluded that evidence was insufficient to determine whether the effects of iontophoresis for the treatment of hyperhidrosis exceed those of placebo. (2) The 2003 TEC Assessment also concluded that, in the treatment of hyperhidrosis, there is insufficient evidence to show that tap water iontophoresis is as beneficial as topical drug administration. The conclusion from the rationale of the TEC Assessment that originally suggested that iontophoresis could be considered medically necessary is now considered investigational.

Additional literature also suggests that the efficacy for iontophoresis ranges from 80-90%. The main limitation of this therapeutic modality is that it is time consuming and may cause skin irritation, dryness or peeling. Sweating is well controlled after 6-10 treatments, however, long-term maintenance therapy is generally required at 1 to 4 week intervals. Iontophoresis is considered a second line treatment for palmar or plantar hyperhidrosis, following aluminum chloride antiperspirants.

Botulinum toxin

Botulinum toxin is a potent neurotoxin that blocks cholinergic nerve terminals; symptoms of botulism include cessation of sweating. Therefore, intracutaneous injections have been investigated as a treatment of gustatory hyperhidrosis and focal primary hyperhidrosis, most frequently involving the axillae or palms. Laskawi and colleagues reported on the outcomes of 19 patients with gustatory hyperhidrosis treated with botulinum toxin injected into every 4 cm² of involved skin. (3) In all cases, gustatory sweating ceased within 2 days, with a mean duration of effect of 17 months. There is a considerable body of published literature regarding botulinum toxin injection of the treatment of axillary hyperhidrosis, all of which substantiates its effectiveness. (4-13) The drawback of this approach is the need for repeated injections, which have led some to consider surgical approaches, discussed below.

Lowe et al (2007) published the results of a double-blind, randomized, placebo-controlled study of efficacy and safety for the use of botulinum toxin type A in the treatment of primary axillary hyperhidrosis. Three hundred twenty-two subjects of at least 18 years of age and diagnosed with bilateral primary axillary hyperhidrosis were randomized to the use of botulinum toxin A or placebo in this 52-week, multicenter study. Botulinum toxin A significantly reduced daily limitations at 4 weeks after injection. The median duration of effect was 197 days and was well tolerated. The 4-point Hyperhidrosis Disease Severity Scale (HDSS) was used to evaluate the level of disease. Botulinum toxin A effectively reduces the symptoms of primary axillary hyperhidrosis. Limitations were cited as the effect of total surface area involvement on treatment efficacy was not evaluated.

Endoscopic Transthoracic Sympathectomy

Eccrine sweat glands produce an aqueous secretion, the overproduction of which is primarily responsible for hyperhidrosis. These glands are innervated by the sympathetic nervous system. Therefore, various surgical techniques of thoracic sympathectomy have been investigated as a curative procedure, primarily for combined palmar and axillary hyperhidrosis. Large case series have reported success rates of up to 98% in large case series, (14-20) A variety of approaches have been reported but endoscopic techniques have emerged as a minimally invasive alternative to either transaxillary, supraclavicular, or anterior thoracic approaches. While accepted as an

effective treatment, sympathectomy is not without complications. In addition to the immediate surgical complications of pneumothorax or temporary Horner's syndrome, compensatory sweating on the trunk can occur in up to 55% of patients, reducing patient satisfaction with the procedure. Gustatory sweating may also occur. Sympathectomy also results in cardiac sympathetic denervation, which in turn can lead to a 10% reduction in the heart rate.

Libson et al (2007) has evaluated of compensatory sweating (CS) in a retrospective review of 60 patients undergoing bilateral T2-T3 thoracoscopic sympathectomy for palmar hyperhidrosis. Only 40 patients responded to a questionnaire and were included in the study. In all patients, both palms were dry at the end of surgery. CS with different severity occurred in 35 of the 40 patients. Six of 40 regretted undergoing the operation due to the extent and severity of the CS seriously affecting the quality of life. Thoracoscopic sympathectomy is a simple procedure with a high success rate as rated by the authors. The authors recommend that careful selection of patients and comprehensive explanation are advisable.

Surgical Removal of Axillary Sweat Glands

Both eccrine and apocrine axillary sweat glands are predominantly located in the superficial subcutis and dermal subcutaneous interface, with scattered eccrine glands located completely in the dermis. Surgical removal has been performed in patients with severe isolated axillary hyperhidrosis. Removal may involve removal of the subcutaneous sweat glands without removal of any skin, limited excision of skin and removal of surrounding subcutaneous sweat glands, or a more radical excision of skin and subcutaneous tissue en bloc. (21) Depending on the completeness of surgical excision, the treatment is effective in from 50%–95% of patients. Liposuction has also been investigated as a minimally invasive technique to surgical excision. In some case, the procedure has been performed to remove the apocrine sweat glands, located deeper in the dermis, and responsible for axillary malodor, which may be referred to as osmidrosis, or bromidrosis if the malodor is also associated with hyperhidrosis. Although this procedure has been performed for several decades, only scattered case reports regarding its effectiveness were identified in a MEDLINE literature search.

Grimalt et al (2006) evaluated the use of topical atropine sulfate for the treatment of axillary hyperhidrosis. Only ten patients were selected to be in the study. Application of a one ml of water and atropine solution was performed for 30 days to the affected area and massaged for 30 seconds. Results were rated using a 1 to 10 scale of satisfaction. Only 2 of the 10 treated patients responded partially to the topical application of atropine sulfate. The authors concluded that focal hyperhidrosis does not improve after the local application of anticholinergic drugs such as atropine sulfate.

August 2009 Update

A literature search was conducted to update this policy. The use of botulinum type A for glandular hypersecretory disorders and the optimal surgical technique for hyperhidrosis continues to be of interest. However, few long-term, randomized clinical comparative trials exist for the treatment of hyperhidrosis conditions.

Technology Assessments and Systematic Reviews

In May 2008, a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology was published. The assessment is an evidence-based review of the safety and efficacy of botulinum neurotoxin type A in the treatment of autonomic and urologic disorders and low back and head pain. The conclusions and recommendations were developed based on the highest level of evidence and put into current clinical context. The literature quality available for the hyperhidrosis indications was as follows: axillary hyperhidrosis (2 randomized controlled studies); palmar hyperhidrosis (1 randomized control trial and several small clinical studies) and gustatory sweating (5 small controlled clinical trials). In conclusion, the American Academy of Neurology (AAN) created guidelines for use of botulinum neurotoxin for the treatment of autonomic disorders and pain. These guidelines include the following recommendations for hyperhidrosis; *axillary hyperhidrosis*, strong evidence supports botulinum toxin type A should be offered as a treatment option; *palmar hyperhidrosis*, good evidence supports botulinum toxin type A should be considered as a treatment option to patients who are unresponsive to topical treatment as an alternative to iontophoresis or sympathectomy; and *gustatory hyperhidrosis*; weak evidence supports botulinum toxin type A as a treatment option for gustatory sweating.

In conclusion, the current evidence evaluating botulinum toxin type A use for gustatory hyperhidrosis as a result of Frey's syndrome includes 4 non-controlled trials; a cohort study and 3 open trials, and 3 case reports all showing favorable treatment outcomes. The patient inclusion criteria was variable across the studies and case reports; ages varied (16 to 87 years); patients had undergone varied types of parotid surgery (i.e., bilateral, partial); not all studies documented gustatory sweating with Minor's starch test as part of the patient screening?; 1 case report and a cohort study included patients who were refractory to topical agents and surgery. In spite of what appears to be promising clinical efficacy and safety, there are no randomized controlled trials or head-to-head comparisons with other treatment options and numerous limitations in the current evidence. These limitations include small study group size and variability in patient inclusion and exclusion criteria, dose (which makes it difficult to assess the optimal one), outcomes measures for determining clinical efficacy, and follow-up time periods to evaluate long-term efficacy. Therefore, the evidence is insufficient to draw conclusions on the short- and long-term clinical effectiveness of botulinum type A for gustatory hyperhidrosis as a result of Frey's syndrome.

Review articles by Clayman et al and deBree describe the various medical and surgical treatments for Frey's syndrome. Tympanic neurectomy is described as a treatment for Frey's syndrome with satisfactory control reported in 82% of patients. In addition, this surgical treatment is generally definitive without a need for repeated interventions.

A randomized, controlled comparative trial included only male patients (n=80), with a mean age of 22 years, undergoing bilateral thoracoscopic sympathectomy or sympathetic blockage to treat primary hyperhidrosis. The subjects were divided into four groups depending on the technique used for sympathetic blockage; techniques included resection (n = 20), transection (n = 20), ablation (n = 20), and clipping (n = 20). The primary success rate was 96.3% for isolated palmar hyperhidrosis, 95.7% for palmar and axillary hydrosis, and 66.7% for palmar and face/scalp hyperhidrosis. No recurrence was observed. The overall success rate of the operation was 95%, and the differences among the four groups were not statistically significant. In the

clipping group, the duration of the surgical procedure was significantly shorter than in the other groups. Complication rates were similar among the groups. The postoperative chest roentgenogram revealed pneumothorax in 9 patients, but none of them required intervention. The authors concluded that thoracic endoscopic sympathetic blockage yields similar results irrespective of the surgical technique adopted, conclusions need to be tempered by the size of the study groups. In conclusion, future clinical trials comparing surgical techniques will need to ensure that the procedures are standardized and outcome measures validated for both symptoms of the disease and surgical complications. Finally, the studies must have large numbers of patients and adequate long-term follow-up, if they are to detect differences in results among procedures with very high technical success rates.

A single-center, randomized, open-label, study funded by Allergan was conducted to compare the efficacy and safety of intradermal injections of botulinum toxin type A (BTX-A, Botox[®]) and 20% aluminum chloride (AC, Drysol[™]) topical for the treatment of primary focal axillary hyperhidrosis from baseline to week 4. Subjects (n=50) were men (n=14) and women (n=36) 18 years of age and older (mean age 29.9 years) who were randomized to either BTX-A or AC treatment. Prior to enrollment, more than 90% of the subjects in the study had used over-the-counter antiperspirants and described them as “poor” or “ineffective.” There was no significant difference in Hyperhidrosis Disease Severity Scale (HDSS) score at baseline. The primary endpoint was to determine the incidence of treatment response, as measured by an improvement of 2 or more grades on the HDSS. Participants returned for outpatient follow-up visits at weeks 4, 8, and 12 for an assessment of adverse events, changes in concomitant medications, and to complete two validated questionnaires HDSS, Hyperhidrosis Impact Questionnaire (HHIQ), and questions about irritation (QI), a third questionnaire. Given the very high dropout rate after week 4, the results are summarized here only for week 4 of treatment. Of the 50 subjects enrolled, 45 completed 4 weeks of the study, 22 from the BTX-A group and 23 from the AC group. The subjects in the BTX-A group had a mean change in their HDSS score of -2.42 versus -1.33 in the AC group. The difference in treatment response between the BTX-A and AC groups was not significant. On satisfaction with treatment at week 4, 21 subjects (87.5%) in the BTX-A group described themselves as “very satisfied” as compared with 8(33.3%) in the AC group. To date, this is the only study directly comparing BTX-A with 20% AC for the treatment of moderate to severe axillary hyperhidrosis. However, the conclusions the authors draw, which state that BTX-A is superior to AC treatment in patients, will need further investigation with larger, longer term, randomized, blinded studies to determine if BTX-A would be appropriate as a first-line therapy.

Preliminary studies of botulinum type B (BTX-B) have demonstrated potential to ameliorate focal hyperhidrosis; however, evidence is insufficient to determine the impact on clinical outcomes. Myobloc[™] (botulinum toxin type B, Solstice Neuro) has received FDA approved for the treatment of patients with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with the condition.

Key Words:

Botulinum toxin, treatment of hyperhidrosis, Endoscopic sympathectomy, Gustatory hyperhidrosis, Hyperhidrosis, Iontophoresis, Sweating, excessive, Sympathectomy, thoracic, Thoracoscopic sympathectomy

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

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