APPENDIX to Treatment of Hyperhidrosis Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

Background

Hyperhidrosis may be defined as excessive sweating, beyond a level required to maintain normal body temperature in response to heat exposure or exercise. It can be classified as either primary or secondary. Primary focal hyperhidrosis is idiopathic in nature, typically involving the hands (palmar), feet (plantar), or axillae (underarms). 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.

Secondary hyperhidrosis is usually generalized or craniofacial sweating. Secondary gustatory hyperhidrosis is excessive sweating on ingesting highly spiced foods. This trigeminovascular reflex typically occurs symmetrically on scalp or face and predominately over forehead, lips, and nose. Secondary facial gustatory sweating, in contrast, is usually asymmetrical and occurs independently of the nature of the ingested food. This phenomenon frequently occurs after injury or surgery in the region of the parotid gland. Frey's syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to or surgery near the parotid gland resulting in

damage to the secretory parasympathetic fibers of the facial nerve. After injury, these fibers regenerate, and miscommunication occurs between them and the severed postganglionic sympathetic fibers that supply the cutaneous sweat glands and blood vessels. The aberrant connection results in gustatory sweating and facial flushing with mastication. Aberrant secondary gustatory sweating follows up to 73% of surgical sympathectomies and is particularly common after bilateral procedures.

The consequences of hyperhidrosis are primarily psychosocial in nature. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat production can be assessed with the minor starch iodine test, which is a simple qualitative measure to identify specific sites of involvement.

A variety of therapies have been investigated for primary hyperhidrosis, including topical therapy with aluminum chloride, oral anticholinergic medications, iontophoresis, intradermal injections of botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands. Treatment of secondary hyperhidrosis focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment of menopausal symptoms.

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. The drawback of this approach is the need for repeated injections, which have led some to consider surgical approaches.

Surgical treatment options include removal of the eccrine glands and/or interruption of the sympathetic nerves. 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. Surgical removal has been performed in patients with severe isolated axillary hyperhidrosis.

Various surgical techniques of sympathectomy may also be tried. The second (T2) and third (T3) thoracic ganglia are responsible for palmar hyperhidrosis, the fourth (T4) thoracic ganglion controls axillary hyperhidrosis, and the first (T1) thoracic ganglion controls facial hyperhidrosis. Thoracic sympathectomy has been investigated as a potentially curative procedure, primarily for combined palmar and axillary hyperhidrosis that is unresponsive to non-surgical treatments. 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 generally occurs in a majority of patients, with different degrees of severity. Medical researchers have investigated whether certain approaches (e.g., T3 versus T4 sympathectomy), result in less compensatory sweating, but there remains a lack of consensus about which approach best minimizes the risk of this side effect. In addition, with lumbar sympathectomy for plantar hyperhidrosis, there has been concern about the risk of post-operative sexual dysfunction in men and women.

The outcome of different surgical and medical treatment modalities is best assessed by using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and Minor's starch iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-

specific surveys. Of these, the Hyperhidrosis Disease Severity Scale (HDSS) has been found to have a good correlation to other assessment tools and to be practical in the clinical setting.

Regulatory Status

Drysol™ (aluminum chloride [hexahydrate] 20% topical solution, Person and Covey, Inc.) is approved by the U.S. Food and Drug Administration (FDA) to be used as an aid in the management of hyperhidrosis (axillae, palmar, plantar, and craniofacial); it is available by prescription.

In 2004 the FDA approved botulinum toxin type A (Botox®) to treat primary axillary hyperhidrosis (severe underarm sweating) that cannot be managed by topical agents. In 2009, this product was renamed to OnabotulinumtoxinA. Other FDA-approved botulinum toxin products include:

- 2000: RimabotulinumtoxinB, marketed as Myobloc® (Solstice Neurosciences, San Francisco, CA)
- 2009: AbobotulinumtoxinA, marketed as Dysport® (Medicis Pharmaceutical Corporation, Scottsdale, AZ)
- 2010: IncobotulinumtoxinA, marketed as Xeomin® (Merz Pharmaceuticals, Greensboro, NC)

None of these other botulinum toxin products are indicated for treatment of hyperhidrosis.

On July 31, 2009, the FDA approved the following revisions to the prescribing information of botulinum toxin products:

- A *Boxed Warning* highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection.
- A Risk Evaluation and Mitigation Strategy (REMS) that includes a *Medication Guide* to help patients understand the risk and benefits of botulinum toxin products.
- Changes to the established drug names to reinforce individual potencies and prevent medication errors. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products.

In January 2011, the miraDry® System (Miramar Labs, Inc., Sunnyvale, CA) was cleared by the FDA through the 510(k) process for treating primary axillary hyperhidrosis. This is a microwave device designed to heat tissue at the dermal-hypodermal interface, the location of the sweat glands. Treatment consists of 2 sessions of approximately one hour in duration. Sessions occur in a physician's office and local anesthetic is used.

Iontophoresis

The published literature regarding iontophoresis as a treatment of hyperhidrosis is sparse. A 2003 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment on

iontophoresis concluded that the evidence was insufficient to determine whether the effects of iontophoresis for the treatment of hyperhidrosis exceed those of placebo or an alternative treatment. The TEC Assessment investigators identified only 3 small studies (n=10, 11, and 18, respectively), all of which were conducted in patients with palmar hyperhidrosis.

Since the 2003 TEC Assessment, no randomized controlled trials (RCTs) evaluating tap water iontophoresis for treating hyperhidrosis have been published. Subsequent case series include a study from Ireland with 28 patients (McAleer & Collins, 2013). Patients received a minimum of 9 treatments over 21 days in a clinical setting. Twenty of the 25 patients (80%) for whom data were available after hospital administration of tap water iontophoresis reported a moderate or great amount of improvement in symptoms and a moderate or great improvement in quality of life (according to a Disease Life Quality Index). In addition, a 2014 retrospective case series by Dogruk and colleagues from Turkey, included 21 pediatric patients under age 18. Most of the patients (n=16) had palmoplantar hyperhidrosis. Nineteen patients completed the course of 21 tap water iontophoresis sessions. Among study completers, the mean self-report treatment effectiveness score rated on a 0 to 10 visual analogue scale (VAS) was 6.36 at the end of treatment. Seventeen of 19 patients (89.5%) reported a 50% or more decrease in sweating at the end of treatment.

Section Summary

There is insufficient evidence, consisting of only small case series, that iontophoresis is an effective treatment of hyperhidrosis. Controlled trials are needed to determine whether iontophoresis improves the net health outcome in patients with hyperhidrosis.

Botulinum Toxin Type A

A considerable body of published literature addresses botulinum toxin injection of the treatment of axillary and palmar hyperhidrosis and substantiates the efficacy of this treatment (Flanagan et al., 2008; Heckmann et al., 2001; Lowe et al., 2002; Lowe et al., 2007; Naumann & Lowe, 2001; Naumann et al., 2002; Saadia et al., 2001; Schnider et al., 1997; Talarico-Filho et al., 2007). Studies include multiple randomized placebo-controlled trials evaluating Botox, a botulinum toxin type A product. In addition, another botulinum toxin A product, Dysport, has been evaluated in RCTs for treatment of axillary hyperhidrosis (Heckmann et al., 2001) and palmar hyperhidrosis (Saadia et al., 2001). Moreover, a small RCT published in 2007 by Talarico-Filho and colleagues compared Botox and Dysport and found similar levels of efficacy and safety with the two products.

One of the larger RCTs was published in 2007 by Lowe and colleagues. This study was an industry-sponsored multicenter double-blind, placebo-controlled efficacy and safety study of botulinum toxin type A in patients with persistent bilateral primary axillary hyperhidrosis. Enrollment criteria included a resting sweat production of at least 50 mg/axilla in 5 minutes and a rating of 3 or 4 (underarm sweating barely tolerable or intolerable, and frequently or always interferes with daily activities) on the Hyperhidrosis Disease Severity Scale (HDSS). A total of 322 patients were randomized to receive 50 U, or 75 U of Botox or placebo. Retreatment after 4 weeks was allowed in subjects with at least 50 mg of sweat (per axilla) over 5 minutes and an HDSS score of 3 or 4. Following the first injection, 75% of subjects in the Botox groups showed at least a 2-point improvement in the HDSS, compared with 25% of subjects in the placebo

group. Sweat production decreased by 87% (75 U), 82% (50 U), and 33% (placebo). Similar results were obtained in patients requiring a second treatment. The median duration of effect was 197, 205, and 96 days (75 U, 50 U, and placebo, respectively). Seventy-eight percent of subjects (252) completed the 52-week study; 96 of 110 (87%) in the 75-U group, 83 of 104 (80%) in the 50-U group, and 73 of 108 (68%) in the placebo group. Intent-to-treat analysis at 52 weeks showed a responder rate (greater than 2-point improvement on the HDSS) for 54 (49%) subjects in the 75-U group, 57 (55%) in the 50-U group, and 6 (6%) in the placebo group. Injection-site pain was reported in about 10% of all groups, with a mean duration of 2.4 days (10-day maximum).

No placebo-controlled RCTs were identified evaluating the safety and efficacy of the newest formulation of botulinum toxin A, Xeomin. Two double-blind randomized trials have compared Xeomin to Botox. In 2014, Campanati and colleagues included 25 patients with moderate to severe primary palmar hyperhidrosis resistant to aluminum chloride or iontophoresis. Patients received injections of Xeomin in a randomly selected hand and Botox in the other hand. The botulinum toxin was given at a fixed dosage per cm^2 of the hand. There were no statistically significant differences in outcomes between groups. This included changes in the HDSS and the extent of sweating assessed using the Minor's test. Previously, in 2010, Dressler published a double-blind RCT from Germany comparing Xeomin to Botox for treating primary axillary hyperhidrosis. Forty-six patients with bilateral axillary hyperhidrosis and a previously stable Botox treatment for at least 2 years received 50 MU of Botox in one axilla and 50 MU Xeomin in the other axilla. All patients completed the study. A total of 41 of 46 (89%) patients reported the therapeutic effect as excellent and 5 (11%) as good. The mean reported duration of therapeutic effect was 3.2 months. According to patient self-report in structured interviews, there were no side-to-side differences in therapeutic effect including onset latency, extent, and duration and no differences in injection site pain. Moreover, clinical examination did not identify any side-to-side differences in the diffuse sweating pattern.

There is less evidence in support of botulinum toxin type A for treating plantar hyperhidrosis. No RCTs or large uncontrolled studies were identified; most published studies are case reports or small case series.

The evidence evaluating botulinum toxin A use for gustatory hyperhidrosis as a result of Frey's syndrome includes noncontrolled or nonrandomized studies, all showing favorable treatment outcomes. The patient inclusion criteria were 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.

Section Summary

Multiple RCTs support the efficacy and safety of botulinum toxin A for treating severe axillary and palmar hyperhidrosis. There is a lack of RCTs on use of botulinum toxin A for plantar hyperhidrosis and gustatory hyperhidrosis.

Botulinum Toxin Type B

There was one placebo-controlled randomized trial on botulinum toxin B (Myobloc) for treating primary axillary hyperhidrosis and one on palmar hyperhidrosis. Both studies were by Baumann and colleagues and were published in 2005; neither discussed whether patients had failed previous treatments for hyperhidrosis. The study on axillary hyperhidrosis included 20 participants; they received subcutaneous injections of Myobloc (2,500 U or 0.5 mL per axilla) (n=15) or placebo (n=5). Patients who received placebo were offered Myobloc at subsequent injections. One patient in the placebo group did not return for follow-up and another responded to placebo and did not return for a subsequent Myobloc injection. Data were available on Myobloc efficacy for the remaining 18 participants (15 in the initial Myobloc group and 3 crossovers). There was a statistically significant improvement in axillary hyperhidrosis according to patient and physician subjective assessment from baseline (before receiving an active injection) to Day 30. Details on the efficacy outcomes were not reported. The mean length of time to return to baseline levels of sweating in these 18 patients was 151 days (range: 66 to 243 days). Sixteen participants reported 61 adverse events over the course of the study. Five of 61 adverse events (8.2%) were determined to be definitely related to the study; 4 axillary bruising events, and 1 instance of pain at the injection site. Eleven adverse events (18%) were determined to be probably related to study treatment; dry eyes (n=3), dry mouth (n=5), and indigestion (n=3). Flu-like symptoms were reported by 6 of 20 patients (30%); however, the study period coincided with flu season. Note that the authors did not compare the active treatment and placebo groups in their analysis.

The RCT on Myobloc for treatment of palmar hyperhidrosis included 20 participants with excessive palmar sweating (Baumann et al., 2005). Fifteen participants received injections of Myobloc (50,000 U per palm) and 5 received placebo. Nonresponders were offered an injection of Myobloc at day 30. At day 30, the two quality-of-life measures were significantly higher in the Myobloc group compared to the control group. However, there was not a statistically significant difference in efficacy in the physician analysis of the palmar iodine starch test at day 30; p=0.56. No further details were provided on the efficacy outcome measures described above. The mean duration of action according to self-report in 17 patients (15 in the initial treatment group and 2 who crossed-over from the placebo group) was 3.8 months (range: 2.3 to 4.9 months). Participants were asked about specific adverse events. Eighteen of 20 (90%) reported dry mouth/throat, 12 (60%) reported indigestion, 12 (60%) reported excessively dry hands, 12 (60%) reported muscle weakness, and 10 (50%) reported decreased grip strength. Both studies by Baumann and colleagues were limited by small sample sizes and limited or no comparative data.

A small randomized trial was published by Frasson and colleagues (2011) in Italy that compared botulinum toxin type A and type B for treating axillary hyperhidrosis. This study included 10 patients with idiopathic focal axillary hyperhidrosis that was unresponsive to other non-surgical treatments. Patients received 50 U botulinum toxin A in one axilla and 2,500 U botulinum toxin B in the contralateral axilla. Gravimetry was performed at baseline and follow-up as an objective measurement of sweat production. In addition, the sweat area was photographed. At each follow-up point, the decrease in sweat weight from baseline was significantly greater on the botulinum toxin B side compared to the botulinum toxin A side. For example, after 1 month, the sweat

weight in 5 minutes was 13% of the baseline value on the botulinum toxin A side and 4% of the baseline value on the botulinum toxin B side; p=0.049. By 6 months, the sweat weight returned to 91% of baseline on the botulinum toxin A side and 56% of baseline weight on the botulinum toxin B side; p=0.02. Findings were similar for sweating area. All patients tolerated injections of botulinum toxin types A and B well and none reported systemic adverse effects. The authors commented that this study used a higher dosage of botulinum toxin B than previous studies.

A 2013 RCT by Ibrahim and colleagues compared botulinum toxin B and suction-curettage in 20 patients with primary axillary hyperhidrosis. Patients received 1 treatment in 1 axilla and the other treatment in the contralateral axilla. The primary outcomes were reduction in the sweat rate in resting and exercise-induced states at 3 months. The mean percent reduction in the resting sweat rate at 3 months was 72.1% in the botulinum toxin group and 60.4% in the suction-curettage group; the difference between groups was not statistically significant; p=0.29). Similarly, the exercise-induced sweat rate did not differ between groups at 3 months. The mean percent reduction was 73.8% in the botulinum toxin group and 58.8% in the suction-curettage group; p=0.10. Scores on the validated 4-point HDSS, however, did differ significantly between groups at 3 months and favored botulinum toxin B treatment. The difference in the decrease in HDSS scores between the botulinum toxin and suction-curettage groups at 3 months was 0.80 points; p=0.0002. Although findings of this single small trial are not conclusive, study findings suggest that botulinum toxin B may be at least as effective as suction-curettage for treatment of primary axillary hyperhidrosis.

Section Summary

There are few RCTs evaluating botulinum toxin type B for treating hyperhidrosis. One small placebo-controlled RCT did not clearly demonstrate the efficacy of botulinum toxin type B in patients with palmar hyperhidrosis. Two RCTs support the efficacy of this treatment for patients with axillary hyperhidrosis. An additional RCT in patients with axillary hyperhidrosis compared botulinum toxin type B to suction and curettage, and found that botulinum toxin type B resulted in outcomes that did not differ significantly from suction and curettage.

Microwave Treatment

A 2012 RCT by Glaser and colleagues evaluated a microwave device for treating hyperhidrosis. This device applies microwave energy to superficial skin structures with the intent of inducing thermolysis of the eccrine and apocrine sweat glands. This industry-sponsored double-blind study randomized 120 adults with primary axillary hyperhidrosis in a 2-to-1 ratio to active (n=81) or sham (n=39) treatment. Treatment consisted of 2 sessions, separated by approximately 2 weeks. Patients who responded adequately after 1 session or declined further treatment did not need to undergo the second session, and a third procedure was allowed within 30 days for participants who still had a high level of sweating after 2 sessions. All patients in the sham group had 2 sessions. In the active treatment group, 11 individuals (9%) had only 1 session and 10 (8%) had a third procedure. The primary efficacy endpoint was a score of 1 (underarm sweating never noticeable) or 2 (underarm sweating tolerable) on the HDSS score at the 30-day follow-up; HDSS score at 6 months was a secondary outcome. A total of 101/120 (84%) completed the study. At 30 days, 89% of the active treatment group and 54% of the sham group had an HDSS score of 1 or 2; p<0.001. At 6 months, 67% of the active treatment group and 44% of the sham

group had an HDSS score of 1 or 2; the difference between groups remained statistically significant; p=0.02. Unblinding occurred at 6 months. Twelve-month data were available for the active treatment group only; 69% reported an HDSS score of 1 or 2. There were 45 procedure-related adverse events in 23 (28%) of the active treatment group and 5 (13%) of the sham group. The most frequently reported adverse event was altered sensation; no serious adverse events were reported. Compensatory sweating was reported by 2 individuals in each group and had a mean duration of 52 days. The authors noted that study data provided an opportunity to identify areas for improvement of the treatment protocol including waiting longer between treatments and using a higher dose of energy at the second session.

A 2012 industry-sponsored case series by Hong and colleagues reported on 31 patients with primary axillary hyperhidrosis who were treated with microwave therapy using the miraDry system. All patients had an HDSS score of 3 or 4 at baseline. The primary efficacy outcome, the proportion of patients whose HDSS score decreased to 1 or 2 was 28 (90%) at 6 months and 12 months after treatment. Longer-term skin-related adverse effects (that all resolved over time) were altered sensation in the skin of the axillae (65% of patients, median duration: 37 days) and palpable bumps under the skin of the axillae (71% of patients, median duration: 41 days).

Section Summary

One RCT and case series provide insufficient evidence that microwave treatment improves the health outcome for primary focal hyperhidrosis. The RCT reported short-term benefit of microwave treatment in reducing hyperhidrosis, but also reports a high rate of skin-related side effects such as pain and altered sensation. Additional controlled studies with long-term follow-up in the treatment and control groups, a longer period of blinding, and a consistent treatment protocol are needed to confirm the efficacy of this treatment and to better define the risk/benefit ratio.

Radiofrequency Ablation

A 2013 study by Purtuloglu and colleagues evaluated radiofrequency ablation as a treatment option for patients with severe bilateral palmar hyperhidrosis resistant to conservative treatment. The study was conducted in Turkey and retrospectively reviewed outcomes after radiofrequency ablation (n=48) or transthoracic sympathectomy (n=46). Patients were not randomized to treatment group. After the mean of 15-month follow-up, palmar hydrosis was absent in 36 patients (75%) in the radiofrequency ablation group and 44 patients (96%) in the surgery group. The difference in outcomes was statistically significant between groups, favoring the surgical intervention; p<0.01. Six patients in each group reported moderate or severe compensatory sweating; p=0.78.

Section Summary

One nonrandomized comparative study represents insufficient evidence on radiofrequency ablation as a treatment of hyperhidrosis. In this single available study, radiofrequency ablation was found to be inferior to surgical sympathectomy.

Surgical Interventions

Tympanic Neurectomy for Gustatory Hyperhidrosis

Review articles by Clayman and colleagues (2006) and de Bree and colleagues (2007) 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.

Sweat Gland Excision for Primary Focal Hyperhidrosis

Surgery 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 (Hafner & Beer, 2002). Depending on the completeness of surgical excision, the treatment is effective in 50-95% of patients.

Transthoracic Sympathectomy for Primary Focal Hyperhidrosis

Several RCTs and one meta-analysis have compared different approaches to surgery; there were no sham-controlled RCTs. In 2011, Deng and colleagues published a meta-analysis of data from RCTs and observational studies published to 2010 evaluating thoracoscopic sympathectomy for patients with palmar hyperhidrosis. The authors pooled outcome data from different approaches to sympathectomy (i.e., single-ganglia blockage [T2, T3, or T4], and multi-ganglia blockage [T2-3, T2-4, or T3-4]). (Note: T refers to rib). Based on these analyses, they concluded that T3 (11 studies) and T3-4 (2 studies) had the “best” clinical efficacy (i.e., postoperative resolution of symptoms). The T3 approach resulted in a 97.9% pooled efficacy rate, and the T3-4 approach resulted in a 100% pooled efficacy rate. In the studies for which data were available, the pooled rate of postoperative compensatory sweating was 40% after T3 surgery. Data on compensatory sweating after T3-4 surgery was only available from one study with 60 patients; a pooled analysis could not be performed.

Subsequent RCTs have also compared levels of sympathectomy. For example, a 2011 study by Baumgartner and colleagues included 121 patients with disabling palmoplantar hyperhidrosis. Patients were randomized to receive bilateral sympathectomy over T2 (n=61 patients) or T3 (n=60 patients). Six of 121 (5%) patients, 3 in each group, were considered treatment failures (i.e., had recurrent palmar sweating to a bothersome level). There were no significant differences between groups in the reported subjective change in plantar or axillary sweating after surgery. At 6 months, the mean level of compensatory sweating (0 to 10 severity scale) was 4.7 (standard deviation [SD]=2.7) for the T2 group and 3.8 (SD=2.8) for the T3 group; p=not significant. Similarly, at 1 year, the mean severity rating of compensatory sweating was 4.7 (SD=2.5) in the T2 group and 3.7 (SD=2.8) in the T3 group; p=0.09.

A trial in 2011 by Ishy and colleagues in Brazil compared surgery at the T3 and T4 levels and one by Yuncu et al. (2013) in Turkey compared surgery at the T3 and T3-T4 levels. Ishy et al. included 20 patients with palmar hyperhidrosis. All patients experienced complete bilateral remission of palmary sweating after 1 year of follow-up. The level of compensatory sweating did not differ significantly between groups at 1 week, 1 month, or 6 months; but at 1 year, there was a significantly higher rate in the T3 compared to the T4 group (20/20, 100% in the T3 group and

15/20, 75% in the T4 group; p=0.47). Yuncu and colleagues in 2013 included 60 patients with axillary hyperhidrosis; 17 were assigned to T3-4 surgery and 43 to T3 surgery. There were no significant differences between groups in post-operative satisfaction. At the 1-year follow-up, the incidence of compensatory sweating was lower in the T3 group (79%) than the T3-T4 group (100%).

There are also a large amount of data from case series on transthoracic sympathectomy for treating primary focal hyperhidrosis (Gossot et al., 2003; Han et al., 2002; Leseche et al., 2003; Lin et al., 2002; Smidfelt & Drott, 2011; Wait et al., 2010). Case series generally report high success rates for palmar and axillary hyperhidrosis, although there are potential adverse effects, most commonly compensatory sweating.

For example, in 2010, Wait and colleagues published a retrospective analysis of prospectively collected data on patients who underwent bilateral thoracoscopic sympathectomy for hyperhidrosis. Data were available on 322 of 348 (93%) patients who underwent surgery. Patients' previous use of nonsurgical hyperhidrosis treatments was not reported. Complete resolution of symptoms was reported by 300 of 301 (99.7%) with palmar hyperhidrosis, 136 of 186 (73%) with axillary hyperhidrosis, 27 of 30 (90%) with craniofacial hyperhidrosis, and 19 of 197 (9.6%) with plantar hyperhidrosis. Compensatory sweating was reported by a total of 201 of 322 (62%) patients. The compensatory sweating was severe in 20 (6.2%) patients and mild or moderate in 181 (56.2%) patients. It is worth noting that thoracoscopic sympathectomy was performed in some cases of plantar hyperhidrosis and that there was a low rate of success. In addition, when reporting rates of compensatory sweating, the authors did not distinguish between mild and moderate levels of symptoms, although these could have different clinical implications for the patient.

In 2011, Smidfelt and Drott in Sweden reported on long-term outcomes after transthoracic sympathectomy. Of 3,015 patients who had been treated with endoscopic thoracic sympathectomy for hyperhidrosis and/or facial blushing, 1,700 (56%) responded to a written survey after a mean of 14.6 (SD=2.4) years. A total of 85.1% of respondents reported that they had a satisfactory and lasting effect of the surgery. Sweating and/or blushing recurred and was considered a problem in 8.1%, and 6.9% reported no initial effect or a poor effect. Compensatory sweating was considered troublesome by 299 (17.6%), annoying by 409 (24.1%), severe by 367 (21.6%), and incapacitating by 190 (11.2%). Nearly half of the patients who underwent surgery did not respond to the survey; their outcomes may have been different from those of study respondents.

A 2013 series by de Andrade and colleagues reported on complications after thoracic sympathectomy in 1,731 patients with palmar, axillary or craniofacial hyperhidrosis. Thirty days after surgery, 1,531 (88.4%) patients reported compensatory sweating. Among the 1,531 patients, compensatory sweating was mild in 473 (31%), moderate in 642 (42%) and severe in 416 (27%). Gustatory sweating was reported by 334 of the 1,731 (19%) patients.

Section Summary

RCTs and a meta-analysis of RCTs support the efficacy of transthoracic sympathectomy at various levels for palmar and axillary hyperhidrosis. These data are complemented by case series which have found high efficacy rates, but also high rates of compensatory sweating for these

conditions. There is insufficient evidence in support of transthoracic sympathectomy for treating plantar hyperhidrosis; case series found lower rates of efficacy for plantar compared to axillary or palmar hyperhidrosis, and there are concerns for side effects in sexual functioning. There are insufficient data to conclude that any particular approach to surgery results in lower rates of compensatory sweating.

Endoscopic Lumbar Sympathectomy for Primary Plantar Hyperhidrosis

No RCTs were identified but several case series were identified. A 2009 series by Rieger and colleagues from Austria evaluated surgery results in 90 patients (59 men, 31 women with severe plantar hyperhidrosis). Thirty-seven patients (41%) had only plantar hyperhidrosis, and 53 (59%) had plantar and palmar hyperhidrosis. All patients had previously used other treatments including topical aluminum chloride therapy. There were a total of 178 procedures; 90 on the right side and 88 on the left side. The technique involved resecting a segment of the sympathetic trunk between the third and fourth lumbar bodies together with the ganglia (L3 and/or L4). After a mean follow-up of 24 months (range: 3 to 45), hyperhidrosis was eliminated in 87 of 90 patients (97%). Postoperative neuralgia occurred in 38 (42%) patients between the seventh and eighth day. The pain lasted less than 4 weeks in 11 patients, 1-3 months in 19 patients, 4-12 months in 5 patients, and more than 12 months in 3 patients. Three men reported temporary sexual symptoms; one was incapable of ejaculation for 2 months. None of the women reported postoperative sexual dysfunction.

In 2010, Reisfeld reported on results of a U.S.-based study from a specialized hyperhidrosis clinic in which bilateral endoscopic lumbar sympathectomy was performed in 63 patients with focal plantar hyperhidrosis. There were 13 (21%) male patients and 50 (79%) female patients. A clamping method was used in which clamps were placed at L3 (46.6%), L4 (52.4%), and L2 in one case. There was a learning curve with this procedure, and 5 early cases had to be converted to an open procedure. Fifty-six (89%) of the patients had previously undergone some form of thoracic sympathectomy, and all had tried conservative measures. After a mean follow-up of 7 months, all patients considered their plantar hyperhidrosis symptoms to be “cured” or “improved;” 97% reported “cure.” All of the patients with previous thoracic sympathectomy had some degree of compensatory sweating. After lumbar sympathectomy, 51 of the 56 patients (91%) reported that their compensatory sweating was unchanged. In the 7 patients who did not have a previous thoracic sympathectomy, 1 reported mild and 6 reported moderate compensatory sweating. The authors stated that no sexual problems were reported by the male patients, and they did not discuss possible sexual problems among the female patients.

It is worth noting, that in contrast to earlier concerns about this procedure being associated with risks of permanent sexual dysfunction in men and women, the recent case series did not find any instances of permanent sexual dysfunction. A review from a multi-specialty working group on hyperhidrosis stated that lumbar sympathectomy is not recommended for plantar hyperhidrosis because of associated sexual dysfunction; this article did not cite any data documenting sexual dysfunction (Hornberger et al., 2004). To date, there are very few studies on endoscopic lumbar sympathectomy for focal plantar hyperhidrosis and no comparative studies.

Section Summary

There are insufficient data supporting the safety and efficacy of lumbar sympathectomy for treating primary plantar hyperhidrosis.

Summary

There is insufficient evidence on the efficacy and safety of iontophoresis or microwave treatment for treating hyperhidrosis, and on radiofrequency ablation for palmar hyperhidrosis. There is evidence from randomized trials that botulinum toxin improves the net health outcome for patients with axillary hyperhidrosis and evidence that botulinum toxin A products improve the net health outcome for palmar hyperhidrosis. Due to the limited number of studies and high rates of adverse effects, there is insufficient evidence that botulinum toxin B improves the net health outcome for patients with primary palmar hyperhidrosis There is insufficient evidence on the efficacy of any botulinum toxin products for other types of primary hyperhidrosis, including plantar and secondary hyperhidrosis.

Regarding surgical treatments for hyperhidrosis, data from randomized controlled trials and observational studies show high rates of efficacy of endoscopic transthoracic sympathectomy for primary focal hyperhidrosis, with the exception of plantar hyperhidrosis. There are, however, high rates of compensatory hyperhidrosis which must be considered in the treatment decision. There are insufficient data to draw conclusions on the efficacy of endoscopic lumbar sympathectomy in patients with primary plantar hyperhidrosis.

Practice Guidelines and Position Statements

In 2011, an expert consensus statement on the surgical treatment of hyperhidrosis was published by Cerfolio and colleagues, a task force of the Society of Thoracic Surgeons (STS). The document states that endoscopic thoracic sympathectomy is the treatment of choice for patients with primary hyperhidrosis. They further recommend the following treatment strategies (with R referring to rib and the number to which rib):

- R3 interruption for palmar hyperhidrosis; an R4 interruption is also reasonable. The authors note a slightly higher rate of compensatory sweating with an R3 but R3 is also more effective at treating hyperhidrosis.
- R4 or R5 interruption for palmar-axillary, palmar-axillary-plantar or axillary hyperhidrosis alone; R5 interruption is also an option for axillary hyperhidrosis alone.
- R3 interruption for craniofacial hyperhidrosis without blushing; an R2 and R3 procedure is an option but may lead to a higher rate of compensatory sweating, and also increases the risk of Horner's syndrome.

The National Institute for Health and Care Excellence (NICE) issued guidance in 2014 stating that there is sufficient evidence of the efficacy and safety of endoscopic thoracic sympathectomy (ETS) for primary facial blushing to support the use of the procedure.

In 2008, the American Academy of Neurology (AAN) created guidelines for use of botulinum neurotoxin for the treatment of autonomic disorders and pain (Naumann et al., 2008). These guidelines include the following recommendations for botulinum toxin injection as a treatment of hyperhidrosis:

- Should be offered as a treatment option to patients with axillary hyperhidrosis (Level A)
- Should be considered as a treatment option for palmar hyperhidrosis and drooling (Level B)
- May be considered for gustatory sweating (Level C)
- Considered for gustatory sweating (Level C)

Benefit Application

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. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	15877	Suction assisted lipectomy; trunk
	15878	Suction assisted lipectomy; upper extremity
	32664	Thoracoscopy, surgical; with thoracic sympathectomy
	64650	Chemodenervation of eccrine glands; both axillae
	64653	Chemodenervation of eccrine glands; other area(s) (e.g., scalp, face, neck), per day
	64802	Sympathectomy, cervical
	64804	Sympathectomy, cervicothoracic
	64809	Sympathectomy, thoracolumbar
	64818	Sympathectomy, lumbar
	69676	Tympanic neurectomy
	97033	Application of a modality to 1 or more areas; iontophoresis, each 15 minutes

Type	Number	Description
HCPC	None	
ICD9 Procedure	99.27	Iontophoresis
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Reconstructive Services
- Medication Policies: Botulinum Toxin A and B

Key / Related Searchable Words

- Botulinum toxin
- Endoscopic sympathectomy
- Excessive sweating
- Gustatory hyperhidrosis
- Hyperhidrosis
- Iontophoresis
- Thoracic sympathectomy
- Thoracoscopic sympathectomy

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
2/25/1998	BCBSA Medical Policy adoption	Medical Policy Committee

Effective Date	Action	Reason
6/1/2001	Administrative Review	Administrative Review
12/7/2006	Criteria Revised	Medical Policy Committee
3/1/2007	Administrative Review	Administrative Review
12/10/2008	Policy Title Revision, criteria revised	Medical Policy Committee
7/8/2010	Administrative Review	Administrative Review
10/7/2011	Policy revision without position change	Medical Policy Committee
7/14/2014	Policy title change from Hyperhidrosis Treatment Policy revision with position change	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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