I. Description

Hyperhidrosis, or excessive sweating, can lead to impairments in psychologic and social functioning. Various treatments for hyperhidrosis are available, such as topical agents, oral medications, botulinum toxin, and surgical procedures.

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.

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, 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 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 syndrome, compensatory sweating on the trunk generally occurs in most 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 adverse 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 the Minor 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.

A multispecialty working group defines primary focal hyperhidrosis as a condition that is characterized by visible, excessive sweating of at least 6 months in duration without apparent cause and with at least 2 of the following features: bilateral and relatively symmetric sweating, impairment of daily activities, frequency of at least once per week, age at onset younger than 25 years, positive family history, and cessation of focal sweating during sleep.

In the hyperhidrosis disease severity scale, patients rate the severity of symptoms on a scale of 1-4:
1. My underarm sweating is never noticeable and never interferes with my daily activities.
2. My underarm sweating is tolerable but sometimes interferes with my daily activities.
3. My underarm sweating is barely tolerable and frequently interferes with my daily activities.
4. My underarm sweating is intolerable and always interferes with my daily activities.

Gustatory hyperhidrosis conditions:
- Frey’s syndrome
- Encephalitis
- Syringomyelia
- Diabetic neuropathies
- Herpes zoster parotitis
- Parotid abscess

**Regulatory Status**

Drysol™ (aluminum chloride [hexahydrate] 20% topical solution, Person and Covey) is approved by the 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®; Allergan Pharmaceuticals Ireland) 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)
2009: AbobotulinumtoxinA, marketed as Dysport® (Medicis Pharmaceutical Corporation, Scottsdale, AZ)
2010: IncobotulinumtoxinA, marketed as Xeomin® (Merz Pharmaceuticals)

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. “A Boxed Warning highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection.

B. A Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide to help patients understand the risk and benefits of botulinum toxin products.

C. 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.; Sunnydale, 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.

II. Criteria/Guidelines

A. Treatment of patients with severe hyperhidrosis (hyperhidrosis disease severity scale 3 or 4) is covered (subject to Limitations and Administrative Guidelines) when the patient has a documented history of debilitating hyperhidrosis that prevents him or her from performing essential activities of daily living and employment, or has any of the following medical complications:

1. Acrocyanosis of the hands; or
2. History of recurrent skin maceration with bacterial or fungal infections; or
3. History of recurrent secondary infections; or
4. History of persistent eczematous dermatitis in spite of medical treatments with topical dermatological or systemic anticholinergic agents.

B. Specific treatments for the primary focal hyperhidrosis regions listed below are covered (subject to Limitations and Administrative Guidelines) when all of the criteria listed in A above are met as well as any of the following specific criteria relevant to a particular area:

1. Axillary and palmar regions:
**Treatment of Hyperhidrosis**

1. **Axillary region:**
   - Aluminum chloride 20% solution*;
   - Botulinum toxin for severe** primary axillary hyperhidrosis that is inadequately managed with topical agents*, in patients 18 years and older; and
   - Endoscopic transthoracic sympathectomy (ETS) and surgical excision of axillary sweat glands, if conservative treatment (i.e., aluminum chloride or botulinum toxin, individually and in combination) has failed.

2. **Plantar region:** Aluminum chloride 20% solution*

3. **Craniofacial region:**
   - Aluminum chloride 20% solution*; and
   - Endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride) has failed.

C. The following treatments for severe secondary gustatory hyperhidrosis (hyperhidrosis disease severity scale 3 or 4) is covered (subject to Limitations/Exclusions and Administrative Guidelines) when all of the following criteria are met:

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

D. Where hyperhidrosis is secondary to a primary medical condition, that primary condition should be identified and treated wherever possible.

* Aluminum chloride solution is approved by the U.S. Food and Drug Administration (FDA) for treatment of primary hyperhidrosis. At least 1 botulinum toxin product is FDA approved for treatment in adults of severe axillary hyperhidrosis that is inadequately managed by topical agents.

**See HMSA policy for Botulinum Toxin

**III. Limitations**

A. For the majority of patients, treatment of primary hyperhidrosis will not meet HMSA’s payment determination criteria for medical appropriateness based on the lack of an essential functional impairment or medical complications associated with the condition. Treatment of hyperhidrosis for cosmetic reasons is not a benefit of HMSA plans and is therefore ineligible for coverage.

B. The treatments for the following primary focal hyperhidrosis regions listed below are not covered because they are not known to be effective in improving health outcomes:

1. **Axillary region:**
   - Axillary liposuction;
   - Iontophoresis; and
   - Microwave treatment.

2. **Palmar region:**
   - RimabotulinumtoxinB;
   - Iontophoresis;
   - Microwave treatment; and
   - Radiofrequency ablation.

3. **Plantar region:**
   - Botulinum toxin;
   - Iontophoresis;
   - Lumbar sympathectomy; and
d. Microwave treatment.

4. Craniofacial region:
   a. Botulinum toxin;
   b. Iontophoresis; and
   c. Microwave treatment.

C. Botulinum toxin is not covered as a treatment for severe gustatory hyperhidrosis because it is not known to be effective in improving health outcomes.

IV. Administrative Guidelines

Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

ICD-10 codes are provided for your information. These will not become effective until 10/01/2015.

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<td>;other area(s) (e.g., scalp, face, neck), per day</td>
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V. Scientific Background

This policy was originally created in 1999 and was updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through April 15, 2015. Following is a summary of the key literature to date:
Iontophoresis

The published literature regarding iontophoresis as a treatment of hyperhidrosis is sparse. A 2003 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.

Several case series and 1 randomized controlled trial (RCT) were identified in subsequent literature searches. The RCT compared iontophoresis to an alternative intervention and does not provide data on the efficacy of this therapy compared with placebo. In 2014, Rajagopal and colleagues in India compared iontophoresis with botulinum toxin in patients with palmar hyperhidrosis. The trial included 60 patients with a baseline score on the Hyperhidrosis Disease Severity Scale (HDSS) of 3 or 4 (i.e., sweating barely tolerable or intolerable, and frequently or always interferes with daily activities). Patients were randomized to receive treatment with iontophoresis 3 times weekly or 1 botulinum toxin injection in each hand, with 2 weeks between treatments. HDSS scores were recorded at 4 weeks; nonresponders were permitted to crossover to the other treatment arm. At the end of the initial 4 weeks, improvement (defined as decrease of at least 1 point in HDSS score) was identified in 24 (80%) of 30 patients in the botulinum toxin group and 14 (47%) of 30 patients in the iontophoresis group (p=0.007). Sixteen patients in the iontophoresis arm crossed over to the botulinum toxin arm, and 12 of these showed excellent improvement after an additional 4 weeks. In contrast, only 1 of the 6 patients who crossed over from the botulinum toxin arm to the iontophoresis arm showed improvement after a second 4-week treatment period. In this relatively small sample with a relatively short intervention period, iontophoresis was found to be less effective than botulinum toxin.

Among the case series was a 2014 retrospective study from Turkey that included 21 pediatric patients under age 18. Most of the patients (n=16) had palmar hyperhidrosis. Nineteen patients completed the course of 21 tap water iontophoresis sessions. Among study completers, mean self-report treatment effectiveness score rated on a 0-to-10 visual analog scale (VAS) was 6.36 at the end of treatment. Seventeen (89.5%) of 19 patients reported a 50% or more decrease in sweating at the end of treatment. Another representative series was a 2013 study from Ireland that included 28 patients. Patients received a minimum of 9 treatments over 21 days in a clinical setting. Twenty (80%) of the 25 patients 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).

Section Summary
There is insufficient evidence that iontophoresis is an effective treatment of hyperhidrosis. The single RCT found that iontophoresis was less effective than botulinum toxin in the short-term treatment of palmar hyperhidrosis. RCTs are needed to show that iontophoresis is more effective than placebo treatment and/or appropriately designed trials to demonstrate that iontophoresis is at least as effective as alternative therapies.
Botulinum Toxin Type A

A considerable body of published literature addresses botulinum toxin injection for treatment of axillary and palmar hyperhidrosis and substantiates the efficacy of this treatment. 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 and palmar hyperhidrosis. Moreover, a small RCT published in 2007 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. 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 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 (sweating barely tolerable or intolerable, and frequently or always interferes with daily activities) on the 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% (vehicle). (Similar results were obtained in patients requiring a second treatment.) Median duration of effect was 197, 205, and 96 days (75 U, 50 U, and vehicle, respectively). Seventy-eight percent of subjects (n=252) completed the 52-week study; 96 (87%) of 110 in the 75-U group, 83 (80%) of 104 in the 50-U group, and 73 (68%) of 108 in the control group. Intent-to-treat analysis at 52 weeks showed a responder rate (>2-point improvement on the HDSS) in 54 patients (49%) 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 approximately 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. 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 HDSS and the extent of sweating assessed using the Minor test. Previously, in 2010, Dresser et al published an RCT including 46 patients with bilateral axillary hyperhidrosis and a previously stable Botox treatment for at least 2 years.17 Patients received 50 MU of Botox in 1 randomly selected 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 between-group 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.

Evidence evaluating botulinum toxin A use for gustatory hyperhidrosis as a result of Frey syndrome includes uncontrolled or nonrandomized studies, all showing favorable treatment outcomes. The patient inclusion criteria were variable across the studies and case reports; ages varied (16-87 years); patients had undergone varied types of parotid surgery (i.e., bilateral, partial); and not all studies documented gustatory sweating with Minor 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**

One placebo-controlled, randomized trial evaluated botulinum toxin B (Myobloc) for primary axillary hyperhidrosis and one for palmar hyperhidrosis. Both studies were by Baumann and colleagues in the United States and were published in 2005; neither discussed whether patients had failed previous treatments for hyperhidrosis. The axillary hyperhidrosis trial included 20 patients who received subcutaneous injections of Myobloc (2500 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, 3 crossovers). There was a statistically significant improvement in axillary hyperhidrosis from baseline (before receiving an active injection) to day 30, according to patient and physician assessment. 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, 66-243 days). Sixteen participants reported 61 adverse events over the course of the study. Five (8%) of 61 adverse events 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 (30%) of 20 patients; however, the trial 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. 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
Treatment of Hyperhidrosis

according to self-report in 17 patients (15 in the initial treatment group, 2 who crossed over from the placebo group) was 3.8 months (range, 2.3-4.9 months). Patients were asked about specific adverse events: 18 (90%) of 20 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 a small sample sizes and limited or no comparative data.

Frasson and colleagues (2011) in Italy conducted a small randomized trial to compare 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 nonsurgical treatments. Patients received 50 U botulinum toxin A in one axilla and 2500 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 with 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 trial used a higher dosage of botulinum toxin B than previous studies.

A 2013 RCT by Ibrahim and colleagues in the U.S. 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. Primary outcomes were reduction in the sweat rate in resting and exercise-induced states at 3 months. The mean percent reduction in resting sweat rate at 3 months was 72.1% in the botulinum toxin group versus 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 groups at 3 months was 0.80 points (p<0.001). Although findings of this single small trial are not conclusive, they 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 supported the efficacy of this treatment for patients with axillary hyperhidrosis. An additional RCT in patients with axillary hyperhidrosis compared botulinum toxin type B with suction-curettage and found that botulinum toxin type B resulted in outcomes that did not differ significantly from suction-curettage.
Microwave Treatment

A 2012 RCT 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 2:1 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 at the 30-day follow-up; HDSS score at 6 months was a secondary outcome. A total of 101 (84%) of 120 patients completed the study. At 30 days, 89% of the active treatment group versus 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 versus 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 versus 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 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 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 reported 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 evaluated radiofrequency ablation (RFA) 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 RFA (n=48) or transthoracic sympathectomy (n=46). Patients were not randomized to treatment group. After a mean follow-up of 15-months, palmar hydrosis was absent in 36 patients (75%) in the RFA group versus 44 patients (96%) in the surgery group. The difference in outcomes between groups was statistically significant, 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 for RFA as a treatment of hyperhidrosis. In this single available study, RFA 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) described the various medical and surgical treatments for Frey syndrome. Tympanic neurectomy is described as a treatment for Frey 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. 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 surgical approaches; 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 that evaluated thoracoscopic sympathectomy for patients with palmar hyperhidrosis. The authors pooled outcome data from different approaches to sympathectomy, i.e., single-ganglia blockage (T2, T3, T4), and multi-ganglia blockage (T2-3, T2-4, T3-4). (Note: T refers to rib). Based on these analyses, the authors 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 available from only one study with 60 patients; a pooled analysis could not be performed.
Subsequent RCTs have compared levels of sympathectomy. These trials tended to have relatively small sample sizes (i.e., fewer than 100 patients). For example, a 2011 study by Baumgartner and colleagues in the U.S. 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 (5%) of 121 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 (SD) level of compensatory sweating (0-10 severity scale) was 4.7 (2.7) for the T2 group versus 3.8 (2.8) for the T3 group (p=NS). Similarly, at 1 year, the mean (SD) severity rating of compensatory sweating was 4.7 (2.5) in the T2 group versus 3.7 (2.8) in the T3 group (p=0.09). A 2013 trial by Yuncu and colleagues in Turkey 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 postoperative satisfaction. At 1-year follow-up, the incidence of compensatory sweating was less in the T3 group (79%) compared with the T3-4 group (100%).

There also are case series on transthoracic sympathectomy for treating primary focal hyperhidrosis. 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 2014, Karamustafouglu and colleagues in Turkey reported on 80 patients with primary hyperhidrosis (axillary and/or palmar). All 80 patients responded to a questionnaire a mean of 35 months after surgery. Seventy-one (89%) of the 80 patients were very satisfied with the surgical outcome, and the other 11% were dissatisfied. Compensatory sweating was reported by 62 patients (78%). Moreover, a 2013 series reported on complications after thoracic sympathectomy in 1731 patients with palmar, axillary, or craniofacial hyperhidrosis. Thirty days after surgery, 1531 (88%) of patients reported compensatory sweating. Among the 1531 patients, compensatory sweating was mild in 473 (31%), moderate in 642 (42%), and severe in 416 (27%). Gustatory sweating was reported by 334 (19%) of the 1731 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 with axillary or palmar hyperhidrosis, and there are concerns for adverse 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, 3-45), hyperhidrosis was eliminated in 87 (97%) of 90 patients. Postoperative neuralgia occurred in 38 (42%) patients between the seventh and eighth day. The pain lasted less than 4 weeks in 11 patients, 1 to 3 months in 19 patients, 4 to 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 study of bilateral endoscopic lumbar sympathectomy in 63 patients with focal plantar hyperhidrosis who were from a specialized hyperhidrosis clinic in the United States. Thirteen patients (21%) were male, and 50 (79%) were female. A clamping method was used in which clamps were placed at L3 (47%), L4 (52%), 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 patients (89%) 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 (91%) of the 56 patients 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. Male patients reported no sexual problems were reported; investigators did not report 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, these case series did not find any instances of permanent sexual dysfunction. A 2004 review from a multispecialty 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. To date, there are very few studies on endoscopic lumbar sympathectomy for focal plantar hyperhidrosis and no comparative studies.

**Section Summary**
There is insufficient evidence supporting the safety and efficacy of lumbar sympathectomy for treating primary plantar hyperhidrosis.

**Practice Guidelines and Position Statements**

In 2011, a task force of the Society of Thoracic Surgeons published an expert consensus statement on the surgical treatment of hyperhidrosis. 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 issued guidance in 2014 stating that there is sufficient evidence of the efficacy and safety of endoscopic thoracic sympathectomy for primary facial blushing to support the use of the procedure.

In 2008, the American Academy of Neurology created guidelines for use of botulinum neurotoxin for the treatment of autonomic disorders and pain. 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).

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.
VI. References

3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Iontophoresis for Medical Indications. TEC Assessments 2003; Volume 18, Tab 3.